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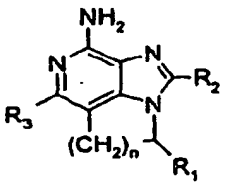
(54) Title: SUBSTITUTED 4H-IMIDAZO [4, 5, 1-IJ] [1, 6] NAPHTHYRIDINE-9-AMINES AND THEIR PHARMACEUTICAL USE



I

(57) Abstract: Substituted 4*H*-imidazo[4,5, 1-*ij*][1,6]naphthyridine-9-amines of the Formula I : pharmaceutical compositions containing the compounds, intermediates, methods of making the compounds, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases, are disclosed.

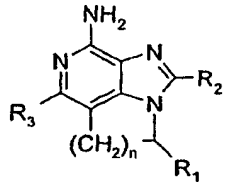
SUBSTITUTED 4*H*-IMIDAZO[4,5,1-*ij*][1,6]NAPHTHYRIDINE-9-AMINES AND METHODS

BACKGROUND

Certain compounds have been found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders. However, there continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other means.

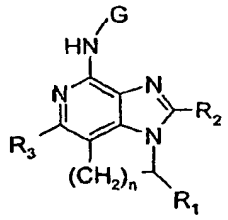
SUMMARY

The present invention provides a new class of compounds, that are useful in inducing cytokine biosynthesis in animals. Such compounds are substituted 4*H*-imidazo[4,5,1-*ij*][1,6]naphthyridine-9-amines of the following Formula I:



I

and compounds of the following Formula II:



II

wherein R_1, R_2, R_3, n and G are as defined below; and include pharmaceutically acceptable salts thereof.

The compounds and salts of Formulas I and II are useful as immune response modifiers (IRMs) due to their ability to modulate cytokine biosynthesis (e.g., induce the biosynthesis or production of one or more cytokines) or otherwise modulate the immune response when administered to animals. The ability to modulate cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing an effective amount of the compounds or salts of Formulas I and II.

In another aspect, the present invention provides methods of inducing cytokine biosynthesis in animal cells, treating a viral disease in an animal, and/or treating a neoplastic disease in an animal by administering to the animal one or more compounds of the Formulas I, II, and/or pharmaceutically acceptable salts thereof.

In another aspect, the invention provides methods of synthesizing the compounds of Formulas I, II, and intermediate compounds useful in the synthesis of these compounds.

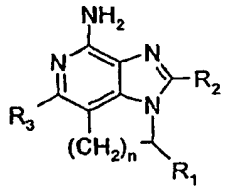
As used herein, "a", "an", "the", "at least one", and "one or more" are used interchangeably.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formulas I and II:



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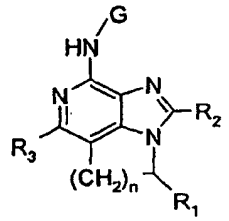
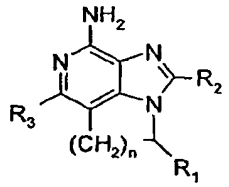


II

wherein R_1, R_2, R_3, n and G are as defined below; and include pharmaceutically acceptable salts thereof.

In one embodiment, the present invention provides a compound of Formula I:



I

wherein:

R_1 is selected from the group consisting of:

-X-R_4,

-X-Y-R_4,

-X-Y-X'-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkoxyalkyl, and hydroxyalkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-8} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkyl;

n is 1, 2, or 3;

X is selected from the group consisting of alkylene, alkenylene, and alkynylene, wherein the alkylene, alkenylene, and alkynylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

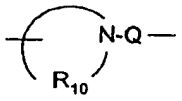
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

$-O-N=C(R_4)-$,

$-C(=N-O-R_8)-$,

$-CH(-N(-O-R_8)-Q-R_4)-$,



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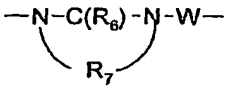

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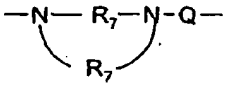

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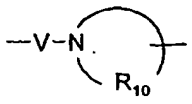

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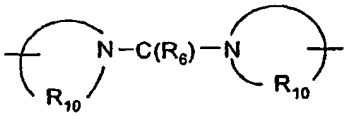
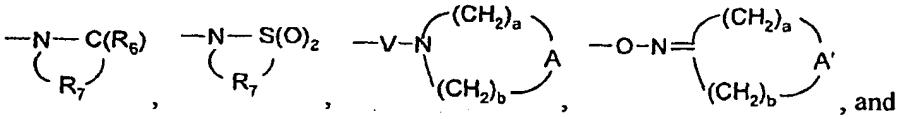


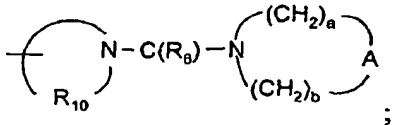
;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; with the proviso that when R_4 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_4 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R_5 is selected from the group consisting of:



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -CH_2-, -O-, -C(O)-, -$S(O)_{0-2}$-, and –N(-Q-R_4)-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

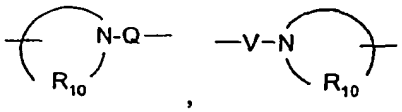
W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

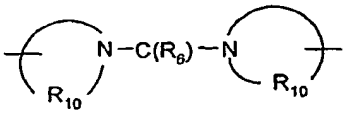
with the proviso that X can also be a bond when:

R_4 is bonded to X; or

Y is bonded to X and Y is -$C(R_6)$-, -$C(R_6)$-O-, -$C(R_6)$-$N(R_8)$-, -$C(R_6)$-$N(OR_9)$-, -C(=N-O-R_8)-, -CH(-N(-O-R_8)-Q-R_4)-,

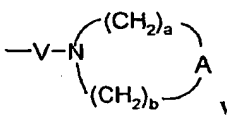


wherein V is -$C(R_6)$-, or

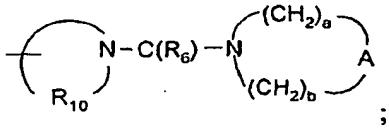


; or

R_5 is bonded to X and R_5 is



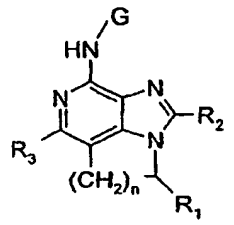
wherein V is -$C(R_6)$- or



;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of Formula II, which is a prodrug:



II

wherein:

G is selected from the group consisting of:

-C(O)-R',

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R',

-C(O)-N(R")R',

-C(=NY')-R',

-CH(OH)-C(O)-OY',

-CH(OC_{1-4} alkyl)Y_0,

-CH_2Y_1, and

-$CH(CH_3)Y_1$;

R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl; and

di-*N*,*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N*,*N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl; and

R_1, R_2, R_3, and n are defined as in Formula I above;

or a pharmaceutically acceptable salt thereof.

For any of the compounds presented herein, each one of the following variables (e.g., X, X', Y, R_1, R_2, R_3, R_4, R_8, G, Q, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments, including embodiments of Formulas I or II, R_1 is selected from the group consisting of -X-R_4, -X-Y-R_4, -X-Y-X'-Y-R_4, and -X-R_5. For certain of these embodiments, R_1 is -X-R_4. For certain of these embodiments, R_4 in -X-R_4 is alkyl which is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, and alkoxy. For certain of these embodiments, R_4 is C_{1-4} alkyl optionally substituted by hydroxy or one or more fluorine atoms. Alternatively, for certain of these embodiments where R_1 is -X-R_4, R_4 is aryl or heteroaryl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and dialkylamino. Alternatively, for certain of these embodiments where R_1 is -X-R_4, R_4 is tetrahydropyranyl.

For certain embodiments, including any one of the above embodiments where R_1 is -X-R_4, X is a bond or alkylene. For certain of these embodiments, X is a bond. Alternatively, for certain of these embodiments, X is -CH_2-.

For certain embodiments, including any one of the above embodiments where R_1 is -X-R_4, except where X is a bond or alkylene, X is alkylene optionally interrupted by one or more -O- groups. For certain of these embodiments, X is C_{2-3} alkylene interrupted by one -O- group.

For certain embodiments, including any one of the above embodiments where R_1 is -X-R_4, except where excluded, R_1 is hydrogen.

For certain embodiments, including any one of the above embodiments where R_1 is -X-R_4, except where excluded, R_1 is methyl.

For certain embodiments, including any one of the above embodiments where R_1 is -X-R_4, except where excluded, R_1 is 4-hydroxybutyl.

For certain embodiments, including any one of the above embodiments where R_1 is -X-R_4, except where excluded, R_1 is tetrahydro-2*H*-pyran-4-yl or (tetrahydro-2*H*-pyran-4-yl)methyl. For certain or these embodiments, R_1 is tetrahydro-2*H*-pyran-4-yl. Alternatively, for certain of these embodiments, R_1 is (tetrahydro-2*H*-pyran-4-yl)methyl.

For certain embodiments, including any one of the above embodiments where R_1 is -X-R_4, except where excluded, R_1 is tetrahydrofuranyl.

For certain embodiments, including any one of the above embodiments of Formulas I or II, except where R_1 is -X-R_4, R_1 is -X-Y-R_4.

For certain embodiments, including any one of the above embodiments of Formulas I or II, except where R_1 is -X-R_4 or -X-Y-R_4, R_1 is -X-Y-X'-Y-R_4.

For certain embodiments, including any one of the above embodiments of Formulas I or II where Y is present, Y is selected from the group consisting of -C(O)-, -$S(O)_2$-, -$N(R_8)$-Q-, or -C(O)-NH-. For certain of these embodiments, including embodiments where Y is -$N(R_8)$-Q-, Q is -C(O)-, -$S(O)_2$, -$S(O)_2$-$N(R_8)$-, or -C(O)-$N(R_8)$-.

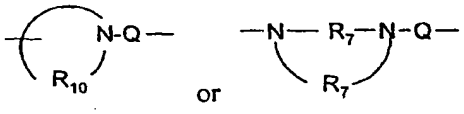
For certain embodiments, including any one of the above embodiments of Formulas I or II where Y-R_4 is present, R_4 in Y-R_4 is alkyl, aryl, arylalkylenyl, or heteroaryl, wherein aryl, arylalkylenyl, and heteroaryl are optionally substituted by alkyl.

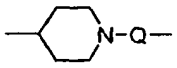
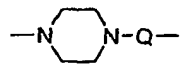
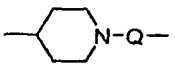
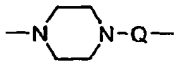
Alternatively, for certain embodiments, including any one of the above embodiments of Formulas I or II where R_1 is -X-Y-R_4, Y is -S-, -$S(O)_2$-, or $N(R_8)$-Q- wherein Q is a bond, -$S(O)_2$-, -C(O)-, -C(O)-O-, -C(O)-$N(R_8)$-, -C(S)-$N(R_8)$-, or -$S(O)_2$-$N(R_8)$-; each R_8 is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxyC_{1-4} alkylenyl, and C_{1-4} alkoxyC_{1-4} alkylenyl; and R_4 is hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and dialkylamino. For certain of these embodiments, Y is -NH-$S(O)_2$-,

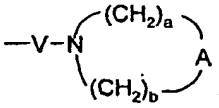
-NH-C(O)-, -NH-S(O)$_2$-N(R_8)-, -NH-C(O)-N(R_8)-, -NH-C(S)-N(R_8)-, -NH-C(O)-O-, or -N(R_8)-; and R_8 is hydrogen, methyl, ethyl, 2-hydroxyethyl, or 2-methoxyethyl. Alternatively, for certain of these embodiments, Y is -S- or -S(O)$_2$-; and R_4 is alkyl or aryl.

For certain of these embodiments, including any one of the above embodiments, except where excluded, X is -(CH_2)$_{1-3}$-.

Alternatively, for certain embodiments, including any one of the above embodiments of Formulas I or II where R_1 is -X-Y-R_4, Y is



; Q is a bond, -C(O)-, -S(O)$_2$-, -S(O)$_2$-N(R_8)-, -C(O)-N(R_8)-, C(S)-N(R_8)-, or -C(O)-O-; R_7 is C_{2-3} alkylene; R_8 is hydrogen or C_{1-4} alkyl; R_{10} is C_{4-6} alkylene; and R_4 in Y-R_4 is hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, and haloalkyl. For certain of these embodiments, Y is  or  . For certain of these embodiments, X is a bond or -CH_2-, and Y is  . For certain of these embodiments, X is -CH_2-. Alternatively, for certain of these embodiments, X is -(CH_2)$_2$-, and Y is  .

For certain embodiments, including any one of the above embodiments of Formulas I or II, except where R_1 is -X-R_4, -X-Y-R_4, or -X-Y-X'-Y-R_4, R_1 is -X-R_5. For certain of these embodiments, X is -(CH_2)$_{1-3}$-. Alternatively, for certain of these embodiments, X is a bond and R_5 is  wherein V is -C(R_6)-.

For certain embodiments, including any one of the above embodiments of Formulas I or II, R_2 is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkoxyalkyl, and hydroxyalkyl. For certain of these embodiments, R_2 is selected

from the group consisting of hydrogen, alkyl, alkoxyalkyl, and hydroxyalkyl. For certain of these embodiments, R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkoxyC_{1-4} alkyl, and hydroxyC_{1-4} alkyl. For certain of these embodiments, R_2 is selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, methoxymethyl, ethoxymethyl, hydroxymethyl, 2-methoxyethyl, and 2-hydroxyethyl.

For certain embodiments, including any one of the above embodiments of Formulas I or II, R_3 is selected from the group consisting of hydrogen, C_{1-8} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkyl. For certain of these embodiments, R_3 is selected from the group consisting of hydrogen and C_{1-8} alkyl. For certain of these embodiments, R_3 is hydrogen, methyl, or ethyl. For certain of these embodiments, R_3 is hydrogen or methyl. For certain of these embodiments, R_3 is hydrogen. Alternatively, for certain of these embodiments, R_3 is methyl. Alternatively, for certain of these embodiments, R_3 is ethyl.

For certain embodiments, including any one of the above embodiments of Formulas I or II, n is 1, 2, or 3. For certain of these embodiments, n is 2. Alternatively, for certain of these embodiments, n is 3.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; with the proviso that when R_4 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when

R_4 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl.

For certain embodiments, R_4 is alkyl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, and alkoxy.

For certain embodiments, R_4 is C_{1-4} alkyl optionally substituted by hydroxy or one or more fluorine atoms.

For certain embodiments, R_4 is aryl or heteroaryl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and dialkylamino.

For certain embodiments, R_4 is tetrahydropyranyl.

For certain embodiments, R_4 is tetrahydro-2*H*-pyran-4-yl.

For certain embodiments, R_4 is tetrahydrofuranyl.

For certain embodiments, R_4 is hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and dialkylamino.

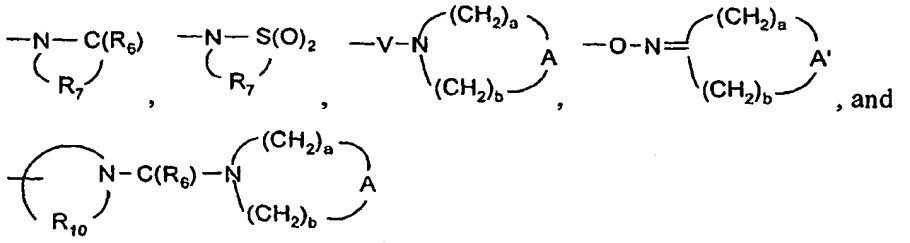
For certain embodiments, R_4 is hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, and haloalkyl.

For certain embodiments, R_4 is alkyl, aryl, arylalkylenyl, or heteroaryl, wherein aryl, arylalkylenyl, and heteroaryl are optionally substituted by alkyl.

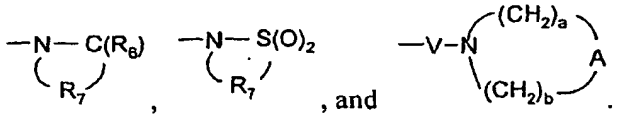
For certain embodiments, R_4 is alkyl or aryl.

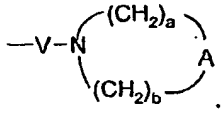
For certain embodiments, R_4 is phenyl.

For certain embodiments, R_5 is selected from the group consisting of:



For certain embodiments, R_5 is selected from the group consisting of:



For certain embodiments, R_5 is  . For certain of these embodiments, V is $-C(R_6)-$. For certain of these embodiments, A is $-CH_2-$, -O-, or $-N(-Q-R_4)-$, and V is -C(O)-. For certain of these embodiments, A is $-CH_2-$, and V is -C(O)-. Alternatively, V is $N(R_8)-C(R_6)-$; A is -O-; a and b are each 2 or 3; and R_8 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_6 is selected from the group consisting of =O and =S.

For certain embodiments, R_6 is =O.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_7 is C_{2-3} alkylene.

For certain embodiments, R_7 is propylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxyC_{1-10} alkylenyl, C_{1-10} alkoxyC_{1-10} alkylenyl, arylC_{1-10} alkylenyl, and heteroarylC_{1-10} alkylenyl.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxyC_{1-4} alkylenyl, and C_{1-4} alkoxyC_{1-4} alkylenyl.

For certain embodiments, R_8 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_8 is hydrogen or methyl.

For certain embodiments, R_8 is hydrogen.

For certain embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_9 is alkyl.

For certain embodiments, R_9 is hydrogen.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, R_{10} is C_{4-6} alkylene.

For certain embodiments, R_{10} is pentylene.

For certain embodiments, A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(-Q-R_4)-$.

For certain embodiments, A is -CH_2-, -O-, or -N(-Q-R_4)-.

For certain embodiments, A is -O-.

For certain embodiments, A is -CH_2-.

For certain embodiments, A is -N(-Q-R_4)-.

For certain embodiments, A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-.

For certain embodiments, A' is -O-.

For certain embodiments, Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-.

For certain embodiments, Q is -C(O)-, -$S(O)_2$, -$S(O)_2$-$N(R_8)$-, or -C(O)-$N(R_8)$-.

For certain embodiments, Q is a bond, -$S(O)_2$-, -C(O)-, -C(O)-O-, -C(O)-$N(R_8)$-, -C(S)-$N(R_8)$-, or -$S(O)_2$-$N(R_8)$-, and each R_8 is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxyC_{1-4} alkylenyl, and C_{1-4} alkoxyC_{1-4} alkylenyl.

For certain embodiments, Q is a bond, -C(O)-, -$S(O)_2$-, -$S(O)_2$-$N(R_8)$-, -C(O)-$N(R_8)$-, -C(S)-$N(R_8)$-, or -C(O)-O-, and R_8 is hydrogen or C_{1-4} alkyl.

For certain embodiments, Q is a bond.

For certain embodiments, V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-.

For certain embodiments, V is -$C(R_6)$-.

For certain embodiments, V is -C(O)-.

For certain embodiments, V is -$N(R_8)$-$C(R_6)$-.

For certain embodiments, V is -$N(R_8)$-C(O)-.

For certain embodiments, W is selected from the group consisting of a bond, -C(O)-, and -$S(O)_2$-.

For certain embodiments, W is a bond.

For certain embodiments, X is selected from the group consisting of alkylene, alkenylene, and alkynylene, wherein the alkylene, alkenylene, and alkynylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group.

For certain embodiments, X is a bond or alkylene.

For certain embodiments, X is a bond or -$(CH_2)_{1-3}$-.

For certain embodiments, X is a bond or -CH_2-.

For certain embodiments, X is a bond.

For certain embodiments, X is -$(CH_2)_{1-3}$-.

For certain embodiments, X is -CH_2- or -$(CH_2)_2$-.

For certain embodiments, X is -CH_2-.

For certain embodiments, X is -$(CH_2)_2$-.

For certain embodiments, X is alkylene optionally interrupted by one or more -O- groups.

For certain embodiments, X is C_{2-3} alkylene interrupted by one -O- group.

For certain embodiments, X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups.

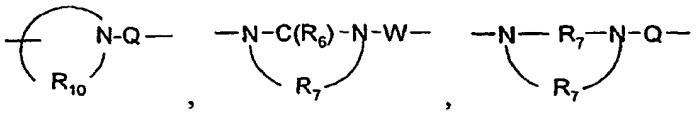
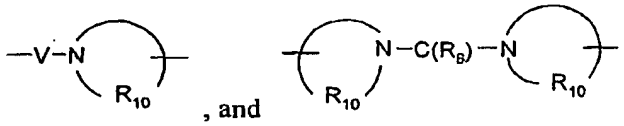
For certain embodiments, X' is alkylene.

For certain embodiments, X' is C_{1-3} alkylene.

For certain embodiments, X' is arylene.

For certain embodiments, X' phenylene.

For certain embodiments, X' is selected from the group consisting of C_{1-3} alkylene and phenylene.

For certain embodiments, Y is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-, -$C(R_6)$-O-, -O-$C(R_6)$-, -O-C(O)-O-, -$N(R_8)$-Q-, -$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, -$C(R_6)$-$N(OR_9)$-, -O-$N(R_8)$-Q-, -O-N=$C(R_4)$-, -C(=N-O-R_8)-, -CH(-N(-O-R_8)-Q-R_4)-,  ,  , and

For certain embodiments, Y is selected from the group consisting of -C(O)-, -$S(O)_2$-, -$N(R_8)$-Q-, or -C(O)-NH-.

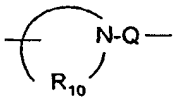
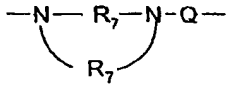
For certain embodiments, Y is selected from the group consisting of -$N(R_8)$-C(O)-, -$N(R_8)$-$S(O)_2$, -$N(R_8)$-$S(O)_2$-$N(R_8)$-, and -$N(R_8)$-C(O)-$N(R_8)$-.

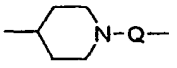
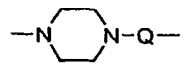
For certain embodiments, Y is -S-, -S(O)$_2$-, -N(R_8)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-, -N(R_8)-C(O)-O-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-C(S)-N(R_8)-, or -N(R_8)-S(O)$_2$-N(R_8)- wherein R_8 is hydrogen, C_{1-4} alkyl, hydroxyC_{1-4} alkylenyl, or C_{1-4} alkoxyC_{1-4} alkylenyl.

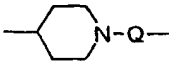
For certain embodiments, Y is -NH-S(O)$_2$-, -NH-C(O)-, -NH-S(O)$_2$-N(R_8)-, -NH-C(O)-N(R_8)-, -NH-C(S)-N(R_8)-, -NH-C(O)-O-, or -N(R_8)- wherein R_8 is hydrogen, methyl, ethyl, 2-hydroxyethyl, or 2-methoxyethyl.

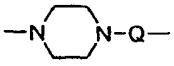
For certain embodiments, Y is -S- or -S(O)$_2$-.

For certain embodiments, Y is -S(O)$_2$-.

For certain embodiments, Y is  or  wherein Q is a bond, -C(O)-, -S(O)$_2$-, -S(O)$_2$-N(R_8)-, -C(O)-N(R_8)-, C(S)-N(R_8)-, or -C(O)-O-; R_7 is C_{2-3} alkylene; R_8 is hydrogen or C_{1-4} alkyl; and R_{10} is C_{4-6} alkylene.

For certain embodiments, Y is  or  .

For certain embodiments, Y is  .

For certain embodiments, Y is  .

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

For certain embodiments, a and b are each 2 or 3.

For certain embodiments, a and b are each 2.

For certain embodiments of the compounds of Formula I or any one of the above embodiments of this Formula, the -NH_2 group can be replaced by an -NH-G group, as shown in the compounds of Formula II, to form prodrugs. In such embodiments, G is selected from the group consisting of -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R', -C(O)-N(R")R', -C(=NY')-R', -CH(OH)-C(O)-OY', -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_1, and -$CH(CH_3)Y_1$. For certain embodiments, G is selected from the group consisting of -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, and -C(O)-O-R'. Preferably, R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl each of which may be

unsubstituted or substituted by one or more substitutents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, haloC_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and -$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen. Preferably, α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids. Preferably, Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl. Preferably, Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxyC_{1-6} alkylenyl, aminoC_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkylenyl. Preferably, Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl.

For certain embodiments, including any one of the above embodiments of Formula II, G is selected from the group consisting of -C(O)-R', α-aminoacyl, and -C(O)-O-R'.

For certain embodiments, including any one of the above embodiments of Formula II, G is selected from the group consisting of -C(O)-R', α-amino-C_{2-11} acyl, and -C(O)-O-R'. α-Amino-C_{2-11} acyl includes α-amino acids containing a total of at least 2 carbon atoms and a total of up to 11 carbon atoms, and may also include one or more heteroatoms selected from the group consisting of O, S, and N.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from an amino acid found in proteins, wherein the the amino acid is selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, the hydroxy hydrogen atom of a hydroxy or hydroxy-containing substituent at the 2-position of Formulas I, II, or any one of the above embodiments of either of these formulas (where a hydroxy or hydroxy-containing substituent is present at the 2-position) is replaced by G' to form a prodrug, wherein G' is selected from the group consisting of α-amino-C_{2-5} alkanoyl, C_{2-6} alkanoyl, C_{1-6} alkoxycarbonyl, and C_{1-6} alkylcarbamoyl.

For certain embodiments, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any

one of Formulas I, II, or any one of the above embodiments of these Formulas and a pharmaceutically acceptable carrier.

For certain embodiments, the present invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of Formulas I, II, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas I, II, or any one of the above embodiments of these Formulas to the animal. For certain of these embodiments, the cytokine is selected from the group consisting of IFN-α, TNF-α, IL-6, IL-10, and IL-12. For certain of these embodiments, the cytokine is IFN-α or TNF-α. For certain of these embodiments, the cytokine is IFN-α.

For certain embodiments, the present invention provides a method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of Formulas I, II, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas I, II, or any one of the above embodiments of these Formulas to the animal.

For certain embodiments, the present invention provides a method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of Formulas I, II, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas I, II, or any one of the above embodiments of these Formulas to the animal.

The term "animal" as used herein includes animals such as, for example, humans, non-human primates, rodents, dogs, cats, horses, pigs, sheep, goats, cattle, and poultry.

As used herein, the terms "alkyl", "alkenyl", "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3

to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "-alkylene-", "alkenylene", "-alkenylene-", "alkynylene", and "-alkynylene-" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms "alkylenyl", "alkenylenyl", and "alkynylenyl" are used when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an "alkylene" moiety to which an aryl group is attached.

Unless otherwise indicated, the term "halogen" refers to a halogen atom or one or more halogen atoms.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. In some embodiments, the term "heteroaryl" includes one ring that contains 2-5 carbon atoms, 1-3 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially

unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. In some embodiments, the term "heterocyclyl" includes one ring that contains 2-5 carbon atoms, 1-3 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

The term "heterocyclyl" includes bicylic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene", "heteroarylene", and "heterocyclylene" are the divalent forms of the "aryl", "heteroaryl", and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene", "heteroarylene", and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, when two R_7 groups are present, each R_7 group is independently selected. In another example, when more than one Y group is present each Y group is independently selected. In another example, when each Y group contains one or more R_8 groups, then, and each R_8 group is independently selected.

The invention is inclusive of the compounds described herein (including intermediates) in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, prodrugs, and the like. In

particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic and scalemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The transformation may occur by various mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritsky, Otto Meth-Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v. 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic

routes may be used to synthesize the compounds of the invention. Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional methods well known to those skilled in the art.

In the preparation of compounds of the invention it may sometimes be necessary to protect a particular functionality while reacting other functional groups on an intermediate. The need for such protection will vary depending on the nature of the particular functional group and the conditions of the reaction step. Suitable amino protecting groups include acetyl, trifluoroacetyl, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl, and 9-fluorenylmethoxycarbonyl (Fmoc). Suitable hydroxy protecting groups include acetyl and silyl groups such as the *tert*-butyl dimethylsilyl group. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, New York, USA, 1999.

Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention, as well as various intermediates related thereto. Such techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

In some of the Reaction Schemes below, the product may be obtained as a racemic or scalemic mixture; particularly, if a racemic starting material is used. A mixture thus prepared can be resolved by methods known to one skilled in the art, for example, by chiral chromatography or by reacting the mixture with an enantiomerically pure sulfonic acid or carboxylic acid and selectively crystallizing a salt of one of the enantiomers from the mixture. In addition, the product in some of the Reaction Schemes below may be obtained as a mixture of diastereomers. A mixture thus prepared can be separated, if desired, by methods known to one skilled in the art, for example, by chromatography or crystallization.

Compounds of the invention can be prepared according to Reaction Scheme I, wherein R_1, R_2, R_3, and n are as defined above, -Hal is –Br or –I, R_{3-1} is $-C_{1-3}alkylOC_1$.

$_4$aklyl or –C_{1-7}alkyl or –H, and R_{1-1} is any R_1 group that does not interfere with the chemistry described in the Reaction Schemes as well as any group that can be converted, as described in greater detail below, into an R_1 group to provide a compound of the invention. In step (1) of Reaction Scheme I, an imidazole is formed from an amine of Formula X. Amines of Formula X can be prepared by known methods or by the methods described below in Reaction Scheme V. Step (1) is conveniently carried out by reacting aminomalonitrile, which is available commercially as the *p*-toluenesulfonic acid salt, with an orthoester of Formula $R_2C(O\text{-alkyl})_3$ to generate an imidate intermediate, which is treated with an amine of Formula X. The orthoester is selected such that it will provide the desired R_2 substituent in a compound of Formula XI. Many orthoesters are commercially available or can be prepared by known methods (for example, the synthesis of ethyl orthoethoxyacetate, $CH_3CH_2OCH_2C(OCH_2CH_3)_3$, is described in McElvain, S. M. and Walters, P. M., *J. Am. Chem. Soc.*, 1942, *64*, 1963). The reaction can be conveniently carried out by heating a solution of aminomalonitrile *p*-toluenesulfonate and the orthoester in a suitable solvent such as tetrahydrofuran (THF) or acetonitrile in the presence of a base such as triethylamine. The solution is allowed to cool to ambient temperature and an amine of Formula X is added. Alternatively, step (1) can be carried out by combining aminomalononitrile *p*-toluenesulfonate with an orthoester of Formula $R_2C(O\text{-alkyl})_3$ in the presence of one equivalent of pyridine and heating at an elevated temperature, for example, 85 °C. The reaction is heated for a time sufficient to form the intermediate imidate, and then an amine of Formula X is added. Heating is continued to provide a compound of Formula XI. Suitable solvents for this reaction include the solvents mentioned above.

In step (2) of Reaction Scheme I, a compound of Formula XI is added to a solution of diiodomethane or bromoform and an alkyl nitrite such as isoamyl nitrite or *tert*-butyl nitrite to yield a compound of Formula XII. The reaction can be carried out at an elevated temperature such as 90 °C, and a co-solvent such as chloroform can be employed.

In step (3) of Reaction Scheme I, a compound of Formula XII undergoes an intramolecular Heck reaction to form a new ring in a compound of Formula XIII. The reaction is conveniently carried out by heating an oxygen-free mixture of a compound of Formula XII, a catalyst such as palladium(II) acetate, a phosphine such as tris(2-

methylphenyl)phosphine, and a base such as triethylamine in a suitable solvent such as dimethylformamide (DMF) at an elevated temperature, for example, 130-140 °C.

In step (4) of Reaction Scheme I, the olefin in a compound of Formula XIII is converted to a ketone with ozone. Ozone is bubbled through a solution of a compound of Formula XIII in a suitable solvent such as dichloromethane at reduced temperature, for example, -78 °C. The reaction is quenched with a reducing agent such as methyl sulfide or triphenylphosphine to afford a ketone of Formula XIV.

In step (5) of Reaction Scheme I, a compound of Formula XIV in which R_{1-1} is an R_1 group that does not interfere with the chemistry described in steps (1) through (5) of Reaction Scheme I (for example, R_1 is $-CH_3$) is treated with ammonia and cyclizes to form a compound of the invention of Formula I. A compound of Formula XIV is treated with ammonia and ammonium acetate. The reaction is carried out in a suitable solvent such as methanol in a sealed pressure vessel at elevated temperature, for example 90 °C. The product of Formula I or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (5a) of Reaction Scheme I, a compound of Formula XIV wherein R_{1-1} is a group that can be converted into an R_1 group to provide a compound of the invention is reacted with ammonia as described in step (5). When R_{1-1} is –X-O-P, a compound of Formula XV is formed wherein X is as defined above and P is a suitable hydroxyl protecting group such as a *tert*-butyldimethylsilyl group. A compound of Formula XV can be used to synthesize compounds of the invention.

In step (6) of Reaction Scheme I, a compound of Formula XV is deprotected to provide a free hydroxyl group in a compound of Formula XVI, which is a subgenus of Formula I. If the protecting group is a *tert*-butyldimethylsilyl group, the deprotection reaction can be carried out with an acid such as acetic acid in a suitable solvent mixture such as THF and water at ambient temperature. Alternatively, the reaction can be carried out with hydrochloric acid in a suitable solvent such as ethanol at ambient temperature. The product of Formula XVI, a compound of the invention, or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In steps (7) and (8) of Reaction Scheme I, a hydroxy-substituted compound of Formula XVI can be converted into an amino-substituted compound of Formula XVIII, which is a subgenus of Formula I. A compound of Formula XVI can be treated with

hydrazoic acid under Mitsunobu reaction conditions to provide an azide-substituted compound of Formula XVII. The reaction can be carried out by adding triphenylphosphine and a solution of hydrazoic acid in toluene to a solution of the hydroxyalkyl-substituted compound in a suitable solvent such as THF or DMF, followed by slow addition of diisopropyl azodicarboxylate. The reaction can be carried out at room temperature and the product of Formula XVII can be isolated using conventional methods. The azido group can then be reduced in step (8) with a reducing agent such as triphenylphosphine in the presence of an acid such as HCl in a suitable solvent mixture such as water/THF to yield an amine-substituted compound of Formula XVIII, which is a compound of the invention.

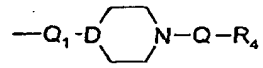
A compound of Formula XVIII can then be converted to an amide, sulfonamide, carbamate, sulfamide, or urea of Formula XIX, i.e. R_{1-2} is -Q-R_4, using conventional methods. For example, a compound of Formula XVIII or salt thereof can react with an acid chloride of Formula $R_4C(O)Cl$ to provide a compound of Formula XIX wherein R_{1-2} is -C(O)-R_4. In addition, a compound of the Formula XVIII can react with a sulfonyl chloride of Formula $R_4S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to provide a compound of Formula XIX wherein R_{1-2} is -$S(O)_2$-R_4. A compound of the Formula XVIII can also react with a chloroformate of Formula $R_4CO(O)Cl$ to provide a compound of Formula XIX in which R_{1-2} is -C(O)-O-R_4. Numerous acid chlorides of Formula $R_4C(O)Cl$, sulfonyl chlorides of Formula $R_4S(O)_2Cl$, sulfonic anhydrides of Formula $(R_4S(O)_2)_2O$, and chloroformates of Formula $R_4CO(O)Cl$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by combining the acid chloride of Formula $R_4C(O)Cl$, chloroformate of Formula $R_4CO(O)Cl$, sulfonyl chloride of Formula $R_4S(O)_2Cl$, or sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ with a compound of Formula XVIII and a base such as triethylamine in a suitable solvent such as chloroform, dichloromethane, or acetonitrile. The reaction can be carried out at room temperature or at a sub-ambient temperature such as 0 °C.

Ureas and thioureas of Formula XIX where R_{1-2} is -$C(R_6)$-$N(R_8)$-W-R_4, wherein W is a bond, R_8 is H, and R_4 and R_6 are as defined above, can be prepared by reacting a compound of Formula XVIII or a salt thereof with isocyanates of Formula $R_4N{=}C{=}O$ or isothiocyanates of Formula $R_4N{=}C{=}S$. Numerous isocyanates and isothiocyanates are

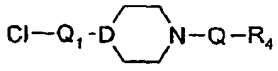
commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the isocyanate or isothiocyanate to a cooled solution of a compound of Formula XVIII in a suitable solvent such as dichloromethane or chloroform. Optionally, a base such as triethylamine can be added. The reaction can be carried out at room temperature or at a sub-ambient temperature such as 0 °C.

Ureas and sulfamides of Formula XIX where R_{1-2} is $-C(R_6)-N(R_8)-W-R_4$ or $-S(O)_2-N(R_8)-R_4$, wherein R_6 is =O, W is a bond, and R_8 and R_4 are as defined above, can be synthesized by treating a compound of Formula XVIII with a carbamoyl chloride of Formula $R_4(R_8)N-C(O)Cl$ or a sulfamoyl chloride of Formula $R_4(R_8)N-S(O)_2Cl$ under the reaction conditions described above for reaction of compounds of Formula XVIII with acid chlorides. In addition, ureas and sulfamides of Formula XIX where R_{1-2} is -C(O)-heterocycle or $-S(O)_2$-heterocycle wherein heterocycle is, for example, pyrrolidine or morpholine, can be prepared from carbamoyl chlorides of Formula Cl-C(O)-heterocycle or sulfamoyl chlorides of Formula $Cl-S(O)_2$-heterocycle. Some carbamoyl chlorides and sulfamoyl chlorides are commercially available; others can be prepared using known synthetic methods from commercially available amines of Formula $HN(R_8)R_4$ or appropriate cyclic amines.

An amide, urea, or sulfamide of Formula XIX where R_{1-2} is



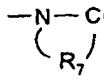
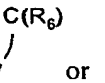
wherein Q_1 is $-C(O)-$ or $-S(O)_2-$, and D is –CH or -N, Q, and R_4 are as defined above can be prepared by treating a compound of Formula XVIII with an acid chloride, carbamoyl chloride, or sulfamoyl chloride of Formula



Some acid chlorides, carbamoyl chlorides, and sulfamoyl chlorides of this formula are commercially available, for example, 1-acetylpiperidine-4-carbonyl chloride and 4-methylpiperazine-1-carbonyl chloride; others can be prepared using known synthetic methods from piperidine-4-carboxylic acid or piperazine. When $-Q-R_4$ is a *tert*-butoxycarbonyl (Boc) in a compound of Formula XIX, the protecting group can be removed under acidic conditions, and the resulting amine can be further elaborated using

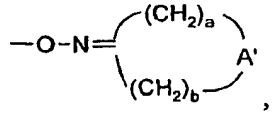
the methods described above to provide a sulfonamide, amide, carbamate, urea, thiourea, or sulfamide.

A compound of Formula XVIII where R_1 is -X-CH_2-NH_2 can be treated with an acid chloride of Formula Cl-R_7C(O)Cl or a sulfonyl chloride of Formula Cl-R_7S(O)$_2$Cl using the reaction conditions described above. The isolable intermediate chloroalkanesulfonamide or chloroalkanamide can then be treated with a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or sodium hydride at room temperature in a suitable solvent such as DMF to effect a cyclization and provide a compound of Formula I in which R_1 is -X-CH_2-R_5, wherein R_5 is

and R_6 and R_7 are as defined above.

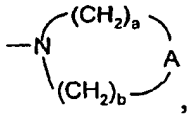
Additional compounds of the invention can be obtained from the hydroxyalkyl-substituted compound of Formula XVI. For example, a compound of Formula XVI can be treated with *N*-hydroxyphthalimide under Mitsunobu reaction conditions to provide an *N*-phthalimide-protected hydroxylamine. The reaction can be conveniently carried out by adding triphenylphosphine and *N*-hydroxyphthalimide to a solution of the hydroxyalkyl-substituted compound in a suitable solvent such as THF or DMF and then slowly adding diisopropyl azodicarboxylate. The reaction can be carried out at room temperature or at an elevated temperature, such as 60 °C. The phthalimide group can then be removed from the resulting *N*-phthalimide-protected hydroxylamine by treatment with hydrazine at room temperature in a suitable solvent such as ethanol. The resulting hydroxylamine can then be treated with one of numerous commercially available aldehydes or ketones in a suitable solvent such as methanol to provide an oxime in a compound of Formula I wherein R_1 is -X-Y-R_4 or -X-R_5, where Y is -O-N=C(R_4)-, R_5 is



, and R_4, a, b, and A' are as defined above. Alternatively, the hydroxylamine prepared after the hydrazine deprotection may be treated with one of numerous acid chlorides, sulfonyl chlorides, isocyanates, carbamoyl chlorides, or sulfamoyl chlorides as described above to provide a compound of the invention of

Formula I wherein wherein R_1 is -X-Y-R_4 where Y is -O-NH-Q-, and Q and R_4 are as defined above.

The alcohol in a compound of Formula XVI can be converted into a chloride group that can be displaced by a nucleophile, such as a cyclic amine of Formula

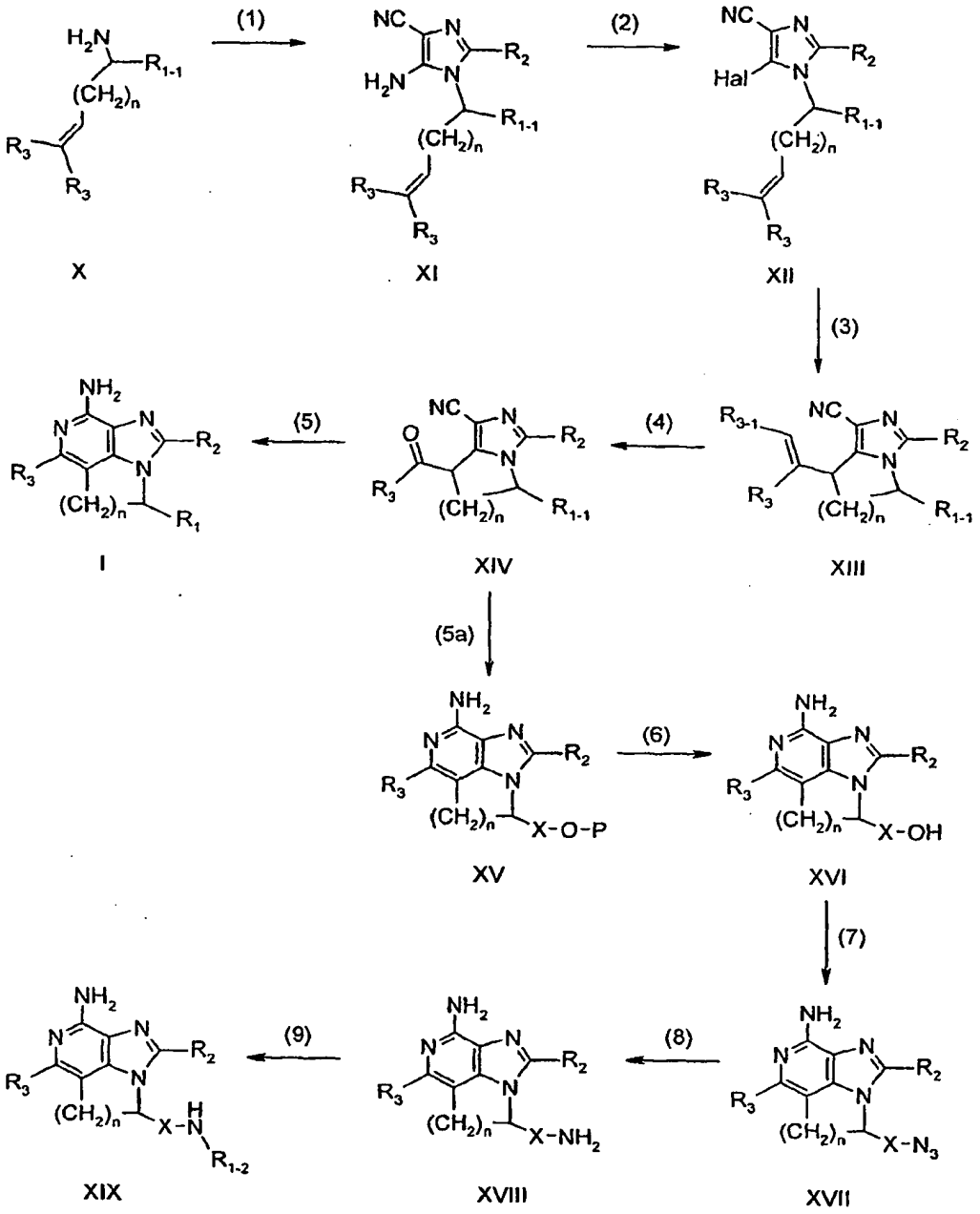


, wherein a, b, and A are as defined above. Several cyclic amines of this formula are commercially available, for example, piperazines that are mono-substitued at the 1-position; others can be prepared by conventional methods. The chlorination reaction can be conveniently carried out by combining a hydroxyl-substituted compound of Formula XVI with thionyl chloride in a suitable solvent such as dichloromethane at room temperature. The resulting chloro-substituted compound is then combined with a cyclic amine in the presence of a base such as potassium carbonate and in a suitable solvent such as DMF. Catalytic sodium iodide can optionally be added. The reaction can be carried out at an elevated temperature such as 50 °C or 90 °C-100 °C. These same reaction conditions also can be used employing a variety of phenols as the nucleophile to provide compounds of Formula I wherein R_1 is -X-Y-R_4 where Y is -O- and R_4 is an unsubstituted or substituted phenyl group. The chloride can also be displaced with a thiol nucleophile, for example, the sodium salt of methanethiol in a suitable solvent such as methanol or ethanol, to provide a sulfide that can be oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to a sulfone of Formula I wherein R_1 is –X-Y-R_4 where Y is –SO_2- and R_4 is –CH_3.

The alcohol in a compound of Formula XVI can be oxidized to an aldehyde that can be converted to an oxime of Formula X-Y-R_4 wherein Y is -C(=N-OR_8)-, and R_8 is as defined above. The reaction can be carried out by combining an aqueous solution of a hydroxylamine salt of Formula NH_2OR_8•HCl and a solution of the aldehyde in a suitable solvent such as methanol or ethanol and then adding a base such as sodium hydroxide and heating at an elevated temperature. The oxime so prepared may be reduced with sodium cyanoborohydride in a mixture of ethanol or methanol in acetic acid to provide a hydroxylamine, which may be treated with one of numerous acid chlorides, sulfonyl chlorides, isocyanates, carbamoyl chlorides, or sulfamoyl chlorides as described above to provide a compound of the invention wherein R_1 is -X-Y-R_4 wherein Y is

-CH(-N-(OR_8)-Q-R_4)-, and Q and R_8 are as defined above. In addition, the aldehyde prepared from the alcohol may also be converted into an alkene using an olefination reaction such as a Wittig or Horner-Emmons reaction. Some of the chemistry described above may require transient protection of the 9-amino group of the 5,6-dihydro-4*H*-imidazo[4,5,1-*ij*][1,6]naphthyridin-9-amine. The 9-amino group of a compound of Formula XV can be protected with a suitable protecting group that is orthogonal to the protecting group on the hydroxyl group. A selective deprotection reaction delivers the free hydroxyl group for subsequent chemical manipulation while the 9-amino group remains protected.

Reaction Scheme I



Compounds of the invention can also be prepared as described in Reaction Scheme II, wherein n, R_{1-1}, R_2, R_3, R_{3-1}, and Hal are as defined above, P is a hydroxyl protecting

group such as a *tert*-butyldimethylsilyl (TBS) group, and R_A is defined below. In step (1) of Reaction Scheme II, an amine of Formula XX is converted into an imidazole of Formula XXI using the reaction conditions described in step (1) of Reaction Scheme I. The synthesis of amines of Formula XX is shown below in Reaction Scheme VI.

In step (2) of Reaction Scheme II, a compound of Formula XXI is transformed into a compound of Formula XXII. The reaction can be performed as described in step (2) of Reaction Scheme I.

In step (3) of Reaction Scheme II, the protecting group is removed from the hydroxyl group in a compound of Formula XXII. If the protecting group is a TBS group, then the deprotection reaction employs an acid such as acetic acid in a suitable solvent mixture such as THF and water to afford an alcohol of Formula XXIII. The reaction is carried out at room temperature, or at elevated temperature (50 °C).

In step (4) of Reaction Scheme II, an alcohol of Formula XXIII is oxidized to an aldehyde of Formula XXIV. The reaction can be carried out using on oxidizing agent such as sulfur trioxide pyridine complex with dimethylsulfoxide (DMSO) and a base such as triethylamine. The reaction can be carried out in a solvent such as DMSO or dichloromethane, or a mixture thereof. The reaction can be carried out at ambient temperature, or at sub-ambient temperature.

In step (5) of Reaction Scheme II, the aldehyde in a compound of Formula XXIV is elaborated into an olefin. The reaction can be carried out using a variety of conditions, depending on which R_3 and R_A groups are desired in a compound of Formula XXV. For example, a compound of Formula XXIV can be reacted with ethyl 2-triphenylphosphoranylidene propionate in a suitable solvent such as dichloromethane at ambient temperature to yield a compound of Formula XXV wherein R_3 is $-CH_3$ and R_A is $-CH_2CH_3$. Alternatively, reaction of a compound of Formula XXIV with ethyl 2-(diethoxyphosphoryl)butanoate with a base such as potassium *tert*-butoxide in a solvent such as THF yields a compound of Formula XXV where R_3 is $-CH_2CH_3$ and R_A is $-CH_2CH_3$.

An intramolecular Heck reaction is used in step (6) of Reaction Scheme II to form a new ring in the compound of Formula XXVI. The reaction can be performed as described in step (3) of Reaction Scheme I.

In step (7) of Reaction Scheme II, a compound of Formula XXVI is hydrolyzed to yield a compound of Formula XXVII. The ester functional group in XXVI is conveniently saponified using a hydroxide base such as lithium hydroxide in a solvent mixture comprised of THF, methanol, and water. The reaction is carried out at ambient temperature.

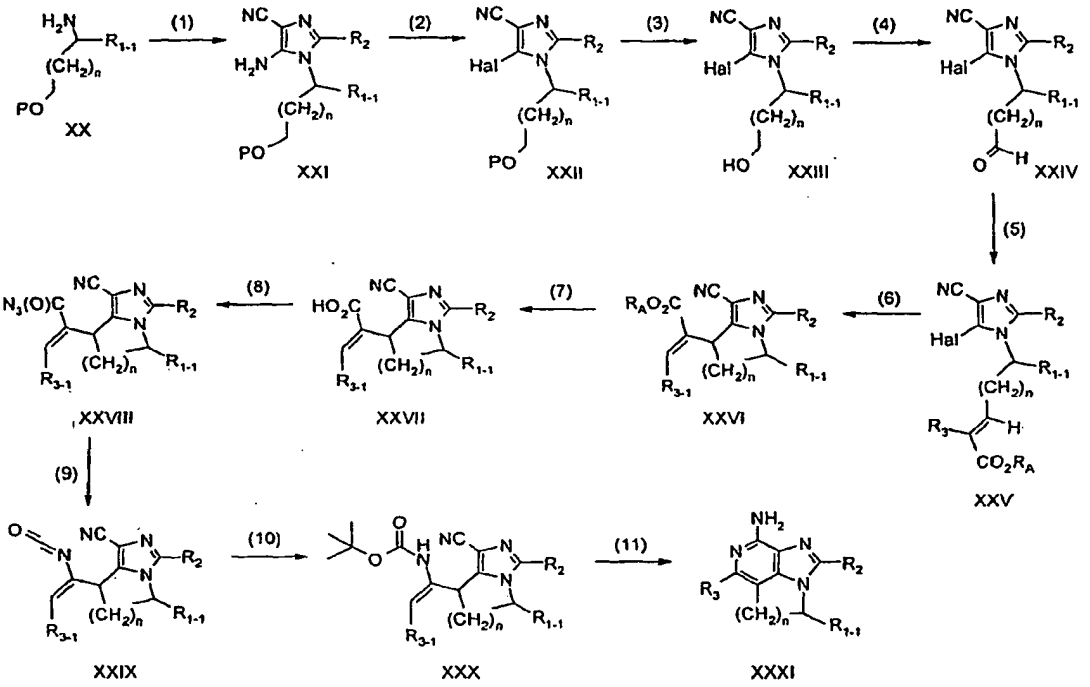
In step (8) of Reaction Scheme II, an acid of Formula XXVII is converted into an acyl azide of Formula XXVIII. The reaction is carried by adding diphenyl phosphoryl azide to a mixture of a compound of Formula XXVII and a base such as triethylamine in a suitable solvent such as THF. The reaction can be carried out at sub-ambient (0 °C) or at ambient temperature.

In step (9) of Reaction Scheme II, an acyl azide of Formula XXVIII undergoes a thermal rearrangement to an isocyanate of Formula XXIX. The reaction is carried out by heating a solution of a compound of Formula XXVIII in a solvent such as toluene at an elevated temperature, for example, 90 °C.

In step (10) of Reaction Scheme II, the isocyanate moiety in a compound of Formula XXIX is converted to a *tert*-butyl carbamate moiety in a compound of Formula XXX. The reaction is carried out by adding *tert*-butanol to the isocyanate at elevated temperature (90 °C) in a suitable solvent such as toluene. Steps (9) and (10) can be carried out sequentially in the same reaction vessel to afford a compound of Formula XXX.

In step (11) of Reaction Scheme II, a compound of Formula XXX is cyclized to form a compound of Formula XXXI. A compound of Formula XXX is treated with a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a suitable solvent such as THF at an elevated temperature, for example 90 °C. Alternatively, a compound of Formula XXIX can be converted directly to a compound of Formula XXXI using the same reaction conditions (DBU, THF, 90 °C). When R_{1-1} is a group that can be converted into an R_1 group, a compound of Formula XXXI can be transformed into a compound of Formula I, for example, as described above in Reaction Scheme I. When R_{1-1} is an R_1 group that is stable to the reaction conditions in Reaction Scheme II, then step (11) directly yields a compound of Formula I. Compounds of Formula XXXI and I or pharmaceutically acceptable salts thereof can be isolated using conventional methods.

Reaction Scheme II



Compounds of the invention may also be prepared as described in Reaction Scheme III, wherein R_{1-1}, R_2 and Hal are as defined above, n = 2, and R_B is $-C(CH_3)_3$ or $-CH_2Ph$. The synthesis starts from a compound of Formula XXIVa, which can be synthesized as shown in Reaction Scheme II. In step (1) of Reaction Scheme III, a compound of Formula XXIVa is converted into a compound of Formula XXXII by applying olefination chemistry similar to that described in step (5) of Reaction Scheme II. Utilization of the reagent methyl (triphenylphosphoranylidene)acetate in dichloromethane provides a compound of Formula XXXII.

In step (2) of Reaction Scheme III, a compound of Formula XXXII undergoes a Heck reaction to yield a compound of Formula XXXIII. The reaction can be carried out using the reaction conditions described above for step (3) of Reaction Scheme I.

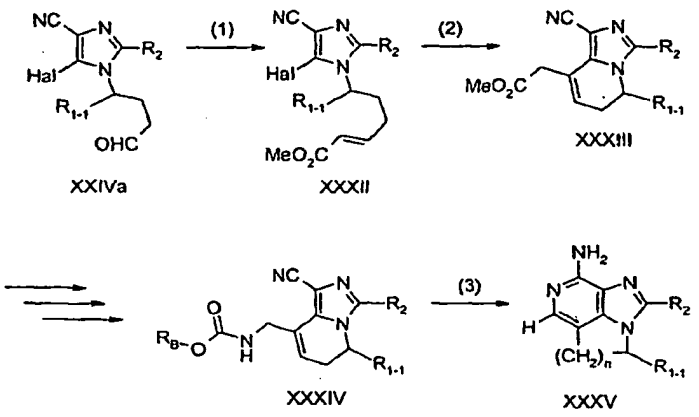
A compound of Formula XXXIII can be converted into a compound of Formula XXXIV wherein R_B is $-C(CH_3)_3$ in three steps by applying the chemistry discussed in

steps (7) – (10) of Reaction Scheme II. Substitution of benzyl alcohol for *tert*-butyl alcohol in the carbamate-forming step gives a compound of Formula XXXIV wherein R_B is $-CH_2Ph$.

In step (3) of Reaction Scheme III, a compound of Formula XXXIV is converted into a compound of Formula XXXV, which is a subgenus of Formula I. A compound of Formula XXXIV wherein R_B is $-CH_2Ph$ is treated under transfer hydrogenation conditions with a catalyst such as 10% palladium on carbon and a hydrogen source such as cyclohexene in a suitable solvent such as methanol at an elevated temperature, for example, the reflux temperature of the solvent, to effect removal of the benzyloxycarbonyl (CBZ) group and afford a primary amine, which is subsequently treated in a second step with an acid such as a solution of hydrogen chloride in diethyl ether in a solvent such as ethanol at elevated temperature (110 °C) to provide a compound of XXXV. Alternatively, a compound of Formula XXXV can be obtained directly following the transfer hydrogenation step. A compound of Formula XXXIV wherein R_B is $-C(CH_3)_3$ can be treated with the acidic conditions described above (HCl, ethanol, 110 °C) to afford a compound of Formula XXXV. When R_{1-1} is a group that can be converted into an R_1 group, a compound of Formula XXXV can be transformed into a compound of Formula I, for example, as described above in Reaction Scheme I. When R_{1-1} is an R_1 group that is stable to the reaction conditions in Reaction Scheme III, for example, an –H group, then step (3) directly yields a compound of Formula I wherein n is 2, and R_1 and R_3 are -H. Compounds of Formula XXXV or pharmaceutically acceptable salts thereof can be isolated using conventional methods.

Finally, the chemistry described in Reaction Scheme III may be applied toward the synthesis of compounds of Formula XXXV wherein n is 1 or 3 and R_{1-1} and R_2 are as described above, from the corresponding aldehydes of Formula XXIV, whose synthesis is described in Reaction Scheme II.

Reaction Scheme III



For some embodiments, compounds of the invention can be prepared according to Reaction Scheme IV wherein R_{1-1}, R_3, and n are as defined in Reaction Scheme I, and R_{2-1} is an alkyl or benzyl group. Compounds of Formula XIa can be prepared by reacting aminomalonitrile or a salt thereof with triphosgene and an amine of Formula X. The reaction can be conveniently carried out in a suitable solvent such as THF in the presence of triethylamine or *N,N*-diisopropylethylamine. See, for example, the method described by Hirota, K. *et al.*, *Heterocycles, 55*, pp. 2279-2282 (2001).

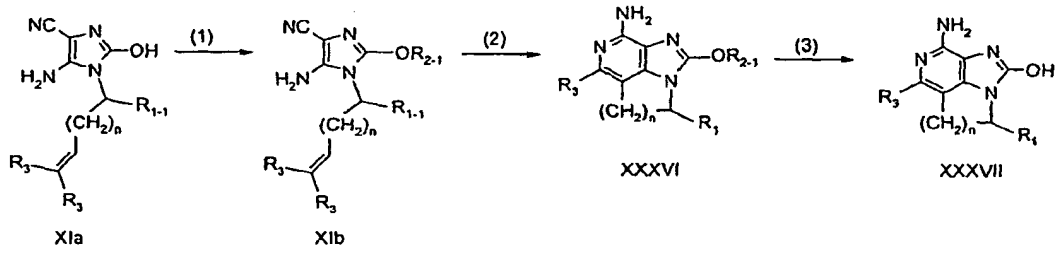
In step (1) of Reaction Scheme IV, a 2-hydroxy imidazole of Formula XIa is converted to an alkyl or benzyl ether to provide an imidazole of Formula XIb. The reaction can be carried out by treating a compound of Formula XIa with an alkyl or benzyl halide in the presence of a base such as potassium carbonate in a suitable solvent such as acetone, methanol, or ethanol. The reaction can be carried out at room temperature or at an elevated temperature such as the reflux temperature of the solvent.

In step (2) of Reaction Scheme IV, a compound of Formula XIb is converted into a compound of Formula XXXVI by using the methods described in steps (2) through (5) of Reaction Scheme I. When R_{2-1} is alkyl, a compound of Formula XXXVI is a compound of the invention of Formula I wherein R_2 is alkoxy, and R_1, R_3, and n are as defined above.

In step (3) of Reaction Scheme IV, a compound of Formula XXXVI is converted to a compound of Formula XXXVII, which is a subgenus of Formula I, using conventional dealkylation methods. For example, a dealkylation reaction can be carried out by treating

a compound of Formula XXXVI wherein R_{2-1} is a C_{1-4} alkyl group with boron tribromide in a suitable solvent such as dichloromethane at room temperature or a sub-ambient temperature such as –78 °C. A compound of Formula XXXVI wherein R_{2-1} is benzyl can be deprotected by hetereogeneous hydrogenation or by treatment with trifluoroacetic acid using conditions known to one of skill in the art. A compound of Formula XXXVII or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IV



Reaction Scheme V describes multiple synthetic routes for an amine of Formula X, which is used in Reaction Scheme I. In Route A, the starting material is a compound of Formula XXXVIIIa where R_D is methyl or ethyl, i.e. commercially available methyl or ethyl acetoacetate. In step (A-1), methyl or ethyl acetoacetate undergoes an alkylation reaction with commercially available 1-bromo-3-methyl-2-butene or 5-bromo-2-methyl-2-pentene to yield a compound of Formula XXXIX where n is 2 or 3, respectively, and R_3 is $-CH_3$. Step (A-1) is conveniently carried out by adding methyl or ethyl acetoacetate to a slurry of sodium hydride in a suitable solvent such as tetrahydrofuran at reduced temperature, for example 0 °C. A base such as *n*-butyl lithium is added to the reaction mixture, followed by the alkenylalkyl bromide to yield a compound of Formula XXXIX, which can be isolated and purified using conventional methods. Not shown in Reaction Scheme V, compounds of Formula XXXIX can be used to make enantiomerically pure amines of Formula X wherein n is 2 or 3, R_3 is $-CH_3$, and R_{1-1} is $-CH_2CO_2CH_3$ or $-CH_2CH_2OP$ using the method described by Overman *et al.* (McDonald, A. I. and Overman, L. E. *J. Org. Chem.* 1999, *64*, 1520-1528; Overman, L. E. *et al. J. Am. Chem. Soc.* 1995, *117*, 2657-2658).

In step (A-2) of Reaction Scheme V, a compound of Formula XXXIX undergoes deprotonation upon treatment with a base such as sodium *tert*-butoxide in a suitable solvent such as an alcohol, for example ethanol or methanol. The deprotonation can be carried out at sub-ambient temperature, for example, 0 °C. The resulting enolate is alkylated with an electrophile of Formula Hal-R_{1-3}, where Hal is -Cl, -Br, or -I, and R_{1-3} is as defined such that $-CH_2R_{1-3}$ is R_{1-1}, to provide a compound of Formula L. The alkylation in step (A-2) is carried out at an elevated temperature, for example, 70 °C, 80 °C, or the reflux temperature of the solvent, optionally with the addition of sodium iodide. Many compounds of Formula Hal-R_{1-3} are available from commercial sources, for example, benzyl bromide, methyl iodide, and ethyl iodide. Other compounds of Formula Hal-R_{1-3} can be synthesized using conventional methods. For example, a compound of Formula Hal-X-OP, wherein X is an alkylene and P is a hydroxyl protecting group, may be synthesized in one step using a conventional method from commercially available reagents of Formula Hal-X-OH, for example, 3-bromopropan-1-ol.

In step (A-3) of Reaction Scheme V, a keto-ester of Formula L undergoes saponification and decarboxylation to afford a ketone of Formula LI. A compound of Formula L is treated with a hydroxide base such as sodium hydroxide in a suitable solvent mixture such as ethanol and water. The reaction is carried out at ambient temperature, then cooled to sub-ambient temperature and quenched with an acid such as hydrochloric acid to afford a ketone of Formula LI.

In step (4) of Reaction Scheme V, a ketone of Formula LI is subjected to a reductive amination reaction to afford an amine of Formula X wherein R_{1-1} is as defined above, R_3 is $-CH_3$, and n is 2 or 3. A ketone of Formula LI is treated with an ammonia source such as ammonium acetate in a suitable solvent such as methanol, optionally in the presence of molecular sieves, to yield an imine that is subsequently reduced with a hydride source such as sodium cyanoborohydride. The reaction can be carried out at ambient temperature.

Alternatively, a ketone of Formula LI can be carried through steps (5) – (8) to afford an amine of Formula X. In step (5), a ketone of Formula LI is reduced with a hydride source such as sodium borohydride or lithium aluminum hydride in a suitable solvent to afford an alcohol of Formula LII. In step (6), the alcohol of Formula LII is converted into a leaving group with a reagent such as *p*-toluenesulfonyl chloride and a

base such as pyridine in a solvent such as dichloromethane at sub-ambient to ambient temperature to afford a compound of Formula LIII, which is reacted with sodium azide in a solvent such as dimethylsulfoxide at elevated temperature, for example 80 °C, in step (7) to afford a compound of Formula LIV. In step (8), the azido group in a compound of Formula LIV is treated with a reducing agent such as triphenylphosphine in a suitable solvent mixture such as water and THF at elevated temperature (45 °C) to afford an amine of Formula X. 6-Methyl-5-heptene-2-ol, a commercially available compound of Formula LII, can be converted to an amine of Formula X, 1,5-dimethylhex-4-enylamine, by applying the chemistry described in steps (6) – (8).

Amines of Formula X can also be synthesized via Route B. In step (B-1) of Route B in Reaction Scheme V, a beta-keto ester of Formula XXXVIII where R_D is an alkyl group and R_{1-1} is as defined above can be alkylated with 1-bromo-3-methyl-2-butene or 5-bromo-2-methyl-2-pentene to yield a compound of Formula LV wherein n_A is 1 or 2, respectively, and R_3 is $-CH_3$. The reaction can be performed using the conditions described above for step (A-2). Many compounds of Formula XXXVIII are commercially available; others can be synthesized using conventional methods.

In step (B-2) of Reaction Scheme V, a compound of Formula LV is transformed into a ketone of Formula LI using the chemistry described in step (A-3). A ketone of Formula LI can be transformed into an amine of Formula X as described above.

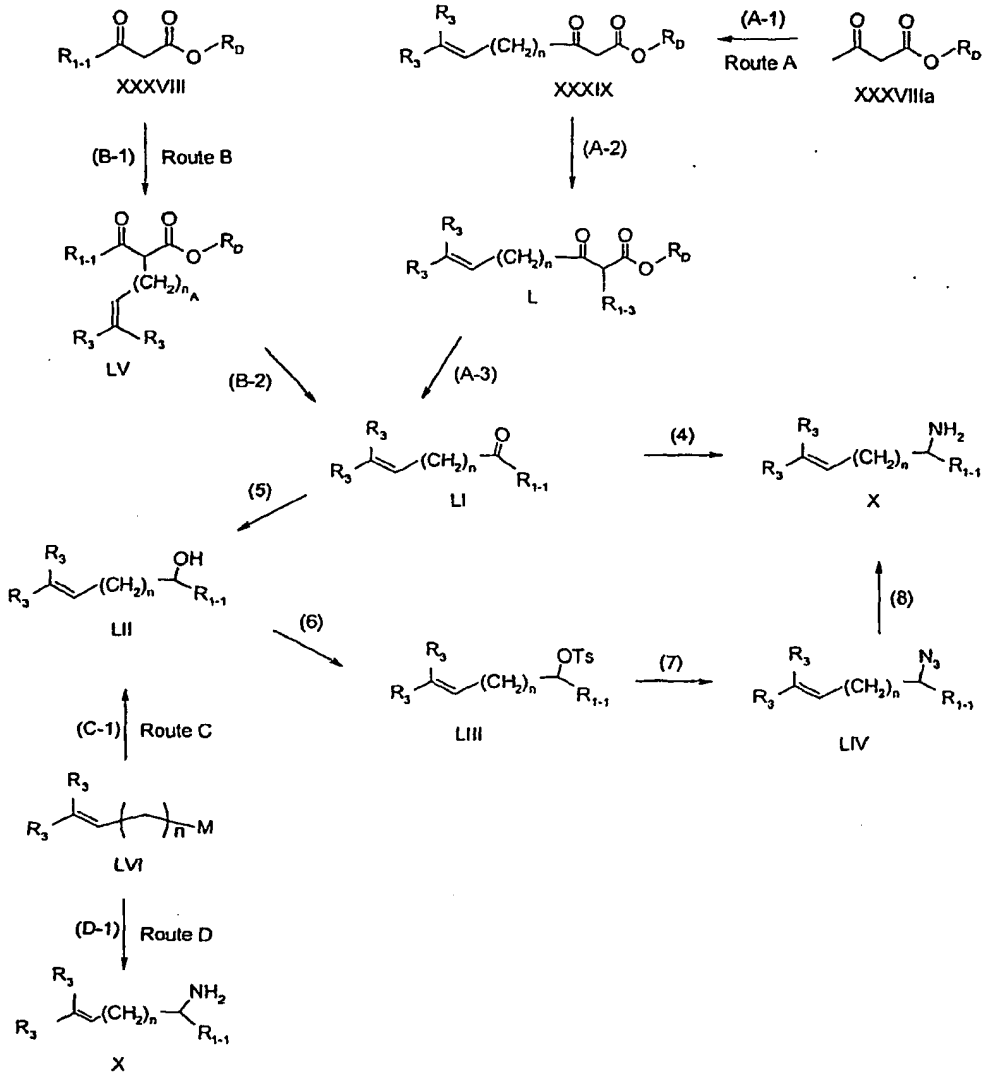
The synthesis of amines of Formula X by Route C or Route D in Reaction Scheme V both start from a organometallic reagent of Formula LVI where M is -Li or -MgBr, n is 1, 2, or 3, and R_3 is $-CH_3$. Organometallic reagents of Formula LVI can be obtained through conventional methods from 1-bromo-3-methyl-2-butene and 5-bromo-2-methyl-2-pentene (commercially available) or 6-bromo-2-methyl-2-hexene (Le Bel, N. A.; Banucci, E. G. *J. Org. Chem.* 1971, *36*, 2400; Matlin A. R. George, C. F.; Wolff, S.; Agosta W. C. J. Am. Chem. Soc. 1986, 108, 3385-3394).

In step (C-1) of Route C, the reagent of Formula LVI adds to an aldehyde of Formula $R_{1-1}CHO$ to form an alcohol of Formula LII where n is 1, 2, or 3, R_3 is $-CH_3$, and R_{1-1} is as defined above. A wide variety of aldehydes of Formula $R_{1-1}CHO$ are commercially available and others can be prepared by known methods. The alcohol of Formula LII can be converted into an amine of Formula X using steps (6) through (8) as

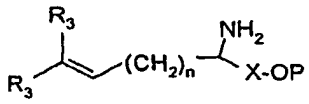
described above. If necessary, a reagent of Formula LVI can be reacted with $CeCl_3$ prior to reaction with an aldehyde.

In step (D-1) of Route D, a reagent of Formula LVI can add to an nitrile of Formula $R_{1-1}CN$ to form an intermediate imine (not shown) that is reduced to yield an amine of Formula X wherein n is 1, 2, or 3, R_3 is $-CH_3$, and R_{1-1} is as defined above. Many nitriles of Formula $R_{1-1}CN$ are commercially available; others can be synthesized using known methods. The reaction can be carried out using known reaction cconditions (Maillard, J. *et al. Bull. Soc. Chim. Fr.* 1967, 2110-2116 and Elphimoff-Felkin *Bull. Soc. Chim. Fr.* 1955, 784-788).

Reaction Scheme V

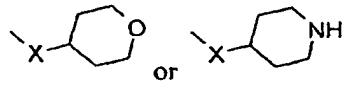


Certain compounds of the invention of Formula XVI (see Reaction Scheme I) wherein X is an alkylene, n is 2 or 3, R_3 is $-CH_3$, and R_2 is as defined above can be synthesized from amines of Formula Xb. Amines of Formula Xb can be synthesized using Route A of Reaction Scheme V, using an alkylating agent of Formula Hal-X-OP, (prepared as described above) in step (A-2).



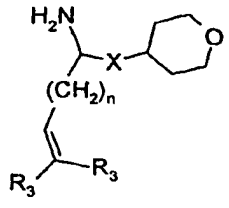
Xb

Certain compounds of the invention of Formula I where R_2 is as defined above, n is 2 or 3, R_3 is $-CH_3$, and R_1 is

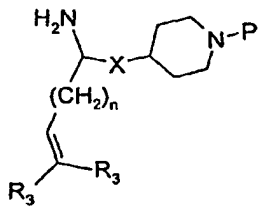


or wherein X is a bond or $-CH_2-$,

can be synthesized as shown in Reaction Scheme I from amines of Formula Xc and Xd below. The synthesis of a compound of Formula I that starts with an amine of Formula Xd, which contains a protected piperidine moiety, includes a deprotection step at an appropriate stage of the synthesis (for example, after step (4) of Reaction Scheme I). A compound of Formula I that contains a piperdine moiety in the R_1 group can be further functionalized using the methods described above in step (9) of Reaction Scheme I to provide additional compounds of the invention.

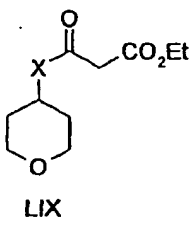


Xc

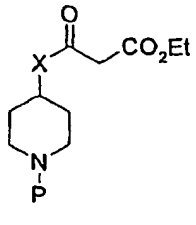


Xd

Amines of Formula Xc and Xd can be synthesized using Route B of Reaction Scheme V starting from commercially or readily available starting materials LIX and LX, wherein X is a bond or $-CH_2-$ and P is a protecting group, for example, a *tert*-butoxycarbonyl (Boc) group.

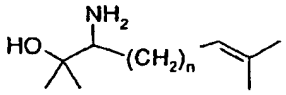


LIX



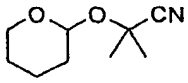
LX

Certain compounds of the invention of Formula I wherein n is 1, 2 or 3, R_3 is $-CH_3$, R_1 is 1-hydroxy-1-methylethyl, and R_2 is as defined above, can be synthesized as described in Reaction Scheme I from an amine of Formula Xe (or a derivative of Formula Xe wherein the hydroxyl group is protected with a suitable protecting group) shown below.



Xe

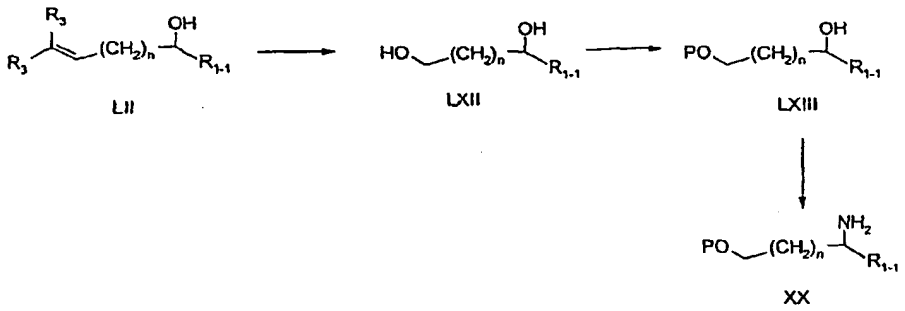
An amine of Formula Xe can be synthesized using Route D of Reaction Scheme V starting from the known tetrahydropyranyl protected cyanohydrin starting material LXI (Maillard, J. *et al. Bull. Soc. Chim. Fr.* 1967, 2110-2116).



LXI

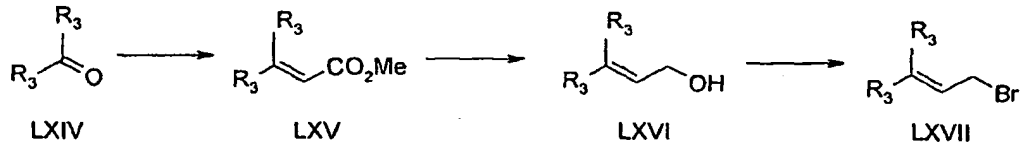
Amines of Formula XX, which are used in Reaction Scheme II, can be prepared as shown in Reaction Scheme VI. A compound of Formula LII, synthesized as described in Reaction Scheme V, is converted to a diol of Formula LXII through treatment with ozone followed by sodium borohydride. The primary alcohol of a compound of Formula LXII is protected selectively with an appropriate protecting group (P), such as a *tert*-butyldimethylsilyl group, to afford a compound of Formula LXIII. The alcohol of Formula LXIII is converted into an amine of Formula XX using the chemistry described in steps (6) through (8) of Reaction Scheme V. Alternatively, amines of Formula XX wherein R_{1-1} is –H and P is *tert*-butyldimethylsilyl can be synthesized from commercially available amino alcohols, for example 4-aminobutanol, using well-known reaction conditions.

Reaction Scheme VI



The synthesis of compounds of Formula I wherein R_3 is $-CH_3$ or $-H$ is well-described above. Additional compounds of the invention of Formula I wherein R_3 is C_{2-8} alkyl or C_{1-4} alkyl-O-C_{1-4}alkyl can be synthesized as shown in Reaction Scheme I from the appropriate amine of Formula X. For example, an amine of Formula X wherein R_3 is C_{2-8} alkyl or C_{1-4} alkyl-O-C_{1-4} alkyl, and n is 1 or 2, can be synthesized by the routes shown in Reaction Scheme V using a compound of Formula LXVII in place of 1-bromo-3-methyl-2-butene. The synthesis of a compound of Formula LXVII, is shown in Reaction Scheme VII. In step (1), a ketone of Formula LXIV wherein R_3 is C_{2-8} alkyl or C_{1-4} alkyl-O-C_{1-4} alkyl is elaborated to an unsaturated ester. Some ketones of Formula LXIV are commercially available, for example, 3-pentanone, 4-heptanone, 5-nonanone, and 1,3-dimethoxyacetone; others can be synthesized using conventional methods. A ketone of Formula LXIV is reacted with an olefination reagent such as dimethoxyphosphoryl acetic acid methyl ester to yield a compound of Formula LXV. A compound of Formula LXV is reduced with a reagent such lithium aluminum hydride or diisobutylaluminum hydride (DIBAL) to yield an alcohol of Formula LXVI, which can be converted into a bromide of Formula LXVII with carbon tetrabromide and triphenylphosphine.

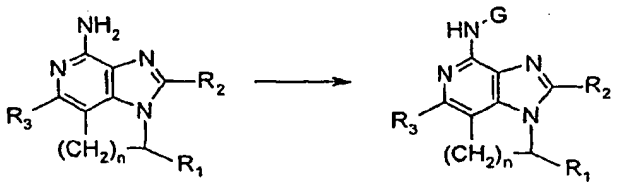
Reaction Scheme VII



LXIV LXV LXVI LXVII

For certain embodiments, compounds of the invention that are prodrugs can be prepared according to Reaction Scheme VIII, wherein R_1, R_2, R_3, n, and G are as defined above. Compounds of Formula I can be prepared according to the methods described above. The 9-amino group of the 5,6-dihydro-4*H*-imidazo[4,5,1-*ij*][1,6]naphthyridin-9-amine of Formula I can be converted using conventional methods to a functional group such as an amide, carbamate, urea, amidine, or another hydrolyzable group by the replacement of a hydrogen atom in an amino group with a group such as -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R', -C(O)-N(R")-R', -C(=NY')-R', -CH(OH)-C(O)-OY', -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_2, or -CH(CH_3)Y_2; wherein R' and R" are each independently C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, or 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, haloC_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and -$S(O)_2$-NH_2; with the proviso that R" may also be hydrogen; each α-aminoacyl group is independently selected from racemic, D, or L-amino acids; Y' is hydrogen, C_{1-6} alkyl, or benzyl; Y_0 is C_{1-6} alkyl, carboxyC_{1-6} alkylenyl, aminoC_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkylenyl, or di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkylenyl; and Y_2 is mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, or 4-C_{1-4} alkylpiperazin-1-yl. Particularly useful compounds of Formula II are amides derived from carboxylic acids containing one to ten carbon atoms, amides derived from amino acids, and carbamates containing one to ten carbon atoms. The reaction can be carried out, for example, by combining a compound of Formula I with a chloroformate or acid chloride, such as ethyl chloroformate or acetyl chloride, in the presence of a base such as triethylamine in a suitable solvent such as dichloromethane at room temperature.

Reaction Scheme VIII



I II

Other prodrugs can be prepared in a variety of ways. For example, a compound wherein R_1 or R_2 is hydroxyalkyl can be converted into a prodrug wherein R_1 or R_2 is, for example, -alkylenyl-O-C(R_6)-R_4, -alkylenyl-O-C(R_6)-O-R_4, or -alkylenyl-O-C(R_6)-N(R_8)-R_4, wherein R_4, R_6, and R_8 are as defined above, using methods known to one skilled in the art. In a compound of Formula I containing an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as C_{1-6} alkanoyloxymethyl, 1-(C_{1-6} alkanoyloxy)ethyl, 1-methyl-1-(C_{1-6} alkanoyloxy)ethyl, C_{1-6} alkoxycarbonyloxymethyl, *N*-(C_{1-6} alkoxycarbonyl)aminomethyl, succinoyl, C_{1-6} alkanoyl, α-aminoC_{1-4} alkanoyl, arylacyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, and α-aminoacyl or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring racemic, D-, and L-amino acids. For compounds containing an alcohol functional group, particularly useful prodrugs are esters made from carboxylic acids containing one to six carbon atoms, unsubstituted or substituted benzoic acid esters, or esters made from naturally occurring L-amino acids. For compounds wherein R_1 or R_2 is hydroxyalkyl, the synthesis can be carried out by treating the compound with a carboxylic acid or amino acid under Mitsunobu reaction conditions in the presence of triphenylphosphine and diisopropyl azodicarboxylate in a suitable solvent such as THF. The reaction can be run at a sub-ambient temperature such as 0 °C.

Compounds of the invention can also be prepared using variations of the synthetic route shown in Reaction Schemes I through IV that would be apparent to one of skill in the art, including variations described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. The exact amount of compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen.

In some embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject.

In other embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, computed according to the Dubois method, in which the body surface area of a subject (m^2) is computed using the subject's body weight: $m^2 = (wt\ kg^{0.425} \times height\ cm^{0.725}) \times 0.007184$, although in some embodiments the methods may be performed by administering a compound or salt or composition in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like. These dosage forms can be prepared with conventional pharmaceutically acceptable carriers and additives using conventional methods, which generally include the step of bringing the active ingredient into association with the carrier.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts described herein

may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful for modulating the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon-α (IFN-α) and tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. The animal to which the compound or salt is administered for induction of cytokine biosynthesis may have a disease as described *infra,* for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts described herein can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts described herein can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-

γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt or composition and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts or compositions identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such as chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a compound or salt identified herein may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts identified herein may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the

disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An animal may also be vaccinated by administering an effective amount of a compound or salt described herein, as a vaccine adjuvant. In one embodiment, there is provided a method of vaccinating an animal comprising administering an effective amount of a compound or salt described herein to the animal as a vaccine adjuvant.

An amount of a compound or salt effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments the induction or inhibition of cytokine biosynthesis may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or composition to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to

about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments either of these methods may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

The methods of the invention may be performed on any suitable subject. Suitable subjects include but are not limited to animals such as but not limited to humans, non-human primates, rodents, dogs, cats, horses, pigs, sheep, goats, or cows.

In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

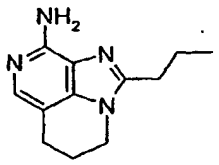
Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

In the examples below automated flash chromatography on silica gel was carried out using a HORIZON HPFC system (an automated high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA) or an INTELLIFLASH Flash Chromatography System (an automated flash purification system available from AnaLogix, Inc, Burlington, Wisconsin, USA). The eluent used for each purification is given in the example. In some chromatographic separations, the solvent mixture 80/18/2 v/v/v chloroform/methanol/concentrated ammonium hydroxide (CMA) was used as the polar component of the eluent. In these separations, CMA was mixed with chloroform in the indicated ratio.

Example 1

2-Propyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-9-amine



Part A

Triethylamine (17.7 mL, 127 mmol), 4-dimethylaminopyridine (70 mg), and *t*-butyldimethylsilyl chloride (18.3 g, 121 mmol) were added to a 0 °C solution of 4-amino-1-butanol (10.3 g, 116 mmol) in dichloromethane (100 mL). The mixture was allowed to warm to room temperature and was stirred for 1 day. The mixture was poured onto water (100 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 21.6 g of 4-{[*tert*-butyl(dimethyl)silyl]oxy}butan-1-amine as an oil that contained minor impurities.

Part B

Trimethyl orthobutyrate (7.35 mL, 45.8 mmol) was added to a solution of aminomalonitrile *p*-toluenesulfonate (11.6 g, 45.8 mmol) and triethylamine (6.4 mL, 46 mmol) in tetrahydrofuran (200) mL at room temperature. The solution was heated at reflux for 35 minutes, then was allowed to cool to room temperature. The solution was cooled to 0 °C and a solution of 4-{[*tert*-butyl(dimethyl)silyl]oxy}butan-1-amine (9.34 g, 45.9 mmol) and triethylamine (6.4 mL) in tetrahydrofuran (50 mL) was added. The reaction was stirred at room temperature for 18 hours, then was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (200 mL) and water (50 mL). The organic phase was washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, gradient elution with 2-4% methanol in dichloromethane) to afford 7.32 g of 5-amino-1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-2-propyl-1*H*-imidazole-4-carbonitrile.

Part C

Isoamylnitrite (10.4 mL, 77.6 mmol) was added over three minutes to a 60 °C (internal temperature) solution of 5-amino-1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-2-propyl-1*H*-imidazole-4-carbonitrile (6.87 g, 20.4 mmol) in diiodomethane (100 mL). There was an exotherm and the internal temperature increased to 80 °C. External heating was applied until the internal temperature reached 100 °C and the brown solution was heated for about 35 minutes. The reaction was allowed to cool to room temperature, and the majority of the diiodomethane was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, eluted with 20% ethyl acetate/hexanes) to afford a solid that was triturated with hexanes and isolated by filtration to provide 2.19 g of 1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-5-iodo-2-propyl-1*H*-imidazole-4-carbonitrile as a orange-yellow solid, mp 88-92 °C. An additional 0.46 g of product was isolated from the filtrate after a second flash column was performed.

Part D

A mixture of 1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-5-iodo-2-propyl-1*H*-imidazole-4-carbonitrile (2.04 g, 4.56 mmol) in acetic acid (40 mL), water (13 mL), and tetrahydrofuran (13 mL) was allowed to stand at room temperature overnight. The yellow solution was concentrated under reduced pressure, and then concentrated from toluene several times, to afford a yellow solid that was dried under vacuum to yield 1.53 g of 1-(4-hydroxybutyl)-5-iodo-2-propyl-1*H*-imidazole-4-carbonitrile.

Part E

Sulfur trioxide pyridine complex (2.90 g, 18.2 mmol) was added to a 0 °C solution of 1-(4-hydroxybutyl)-5-iodo-2-propyl-1*H*-imidazole-4-carbonitrile (1.53 g, 4.56 mmol) and triethylamine (3.18 mL, 22.8 mmol) in dichloromethane (12 mL) and dimethylsulfoxide (24 mL). The reaction was stirred for 1 hour at 0 °C, and more triethylamine (3.18 mL, 22.8 mmol) and sulfur trioxide pyridine complex (2.90 g, 18.2 mmol) were added. After an additional hour at 0 °C, the solution was poured into saturated aqueous ammonium chloride (100 mL) and extracted with diethyl ether (200 mL). The organic layer was washed with water (75 mL) and brine (75 mL). The aqueous layers were back-extracted with diethyl ether. The organic layers were dried separately over magnesium sulfate, filtered, and concentrated under reduced pressure. The material was combined using dichloromethane and concentrated under reduced pressure to afford

1.97 g of 5-iodo-1-(4-oxobutyl)-2-propyl-1*H*-imidazole-4-carbonitrile as a yellow oil, which also contained a small amount of dichloromethane and pyridine. The material was used in the next reaction without purification.

Part F

A solution of crude 5-iodo-1-(4-oxobutyl)-2-propyl-1*H*-imidazole-4-carbonitrile (prepared as described in Part E, approximately 4.56 mmol) and methyl (triphenylphosphoranylidene)acetate (2.29 g, 6.85 mmol) in dichloromethane (15 mL) for 7 hours, then more methyl (triphenylphosphoranylidene)acetate (0.8 g) was added. The solution was allowed to stir overnight. The solution was concentrated under reduced pressure and purified by flash chromatography (silica gel, gradient elution with 30-50% ethyl acetate/hexanes) to afford partially purified product, which was further purified by flash chromatography (silica gel, elution with 30% ethyl acetate/hexanes) to afford 1.27 g of methyl (2*E*)-6-(4-cyano-5-iodo-2-propyl-1*H*-imidazol-1-yl)hex-2-enoate as a yellow oil.

Part G

Nitrogen was bubbled through a solution of methyl (2*E*)-6-(4-cyano-5-iodo-2-propyl-1*H*-imidazol-1-yl)hex-2-enoate (1.26 g, 3.25 mmol) and triethylamine (0.68 mL, 4.88 mmol) in DMF (6.5 mL) in glass pressure vessel. Palladium(II) acetate (18 mg, 0.08 mmol) and tris(2-methylphenyl)phosphine (75 mg, 0.25 mmol) were added and the vessel was sealed with a TEFLON cap. The vessel was heated in a 100 °C bath for 2 hours, then was allowed to cool to room temperature. The reaction mixture was diluted with diethyl ether and washed with water and brine. The aqueous layers were back extracted with diethyl ether. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to yield a brown oil. The crude product was purified by flash chromatography (silica gel, gradient elution with 30-50% ethyl acetate/hexanes) to afford 0.52 g of methyl (1-cyano-3-propyl-5,6-dihydroimidazo[1,5-*a*]pyridin-8-yl)acetate as an off white solid.

Part H

A mixture of methyl (1-cyano-3-propyl-5,6-dihydroimidazo[1,5-*a*]pyridin-8-yl)acetate (0.49 g, 1.89 mmol) and lithium hydroxide (198 mg, 4.72 mmol) in a tetrahydrofuran/water mixture (3:1 ratio, 6.3 mL) was stirred at room temperature for 1 day, then was concentrated under reduced pressure. The residue was partitioned between

0.5 M HCl and ethyl acetate. The aqueous layer was adjusted to pH 3-4 and was extracted with ethyl acetate (2 x). The organic layers were combined, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 0.41 g of (1-cyano-3-propyl-5,6-dihydroimidazo[1,5-*a*]pyridin-8-yl)acetic acid as a white solid.

Part I

Diphenyl phosphoryl azide (0.115 μL, 0.53mmol) was added to a 0 °C solution of (1-cyano-3-propyl-5,6-dihydroimidazo[1,5-*a*]pyridin-8-yl)acetic acid (100 mg, 0.41 mmol) and triethylamine (80 μL, 0.57 mmol) in tetrahydrofuran (4 mL). The solution was allowed to warm to room temperature over 1 hour. The solution was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, gradient elution with 20-40% ethyl acetate in hexanes) to afford 69 mg of (1-cyano-3-propyl-5,6-dihydroimidazo[1,5-*a*]pyridin-8-yl)acetyl azide as a colorless oil.

Part J

A solution of (1-cyano-3-propyl-5,6-dihydroimidazo[1,5-*a*]pyridin-8-yl)acetyl azide (69 mg, 0.26 mmol) in toluene (12 mL) was heated at 90 °C for 1 hour, then was allowed to cool to room temperature. Benzyl alcohol (0.27 mL) was added and the reaction solution was concentrated to about 3 mL. The solution was heated at 100 °C overnight, then was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, gradient elution with 40-80% ethyl acetate/hexanes) to provide 77 mg of benzyl (1-cyano-3-propyl-5,6-dihydroimidazo[1,5-*a*]pyridin-8-yl)methylcarbamate as a colorless oil.

Part K

A mixture of benzyl (1-cyano-3-propyl-5,6-dihydroimidazo[1,5-*a*]pyridin-8-yl)methylcarbamate (about 0.78 g, 2.23 mmol), 10% palladium on carbon (0.35 g), cyclohexene (20 mL), and methanol (20 mL) was heated at reflux under a nitrogen for 25 min. Additional cyclohexene (10 mL) and 10% palladium on carbon (0.27 g) was added and the mixture was heated for an additional 75 min. The mixture was allowed to cool to room temperature and was filtered through CELITE filter agent, which was subsequently rinsed with methanol (150 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography (silica gel, gradient elution with 2-10% methanol in dichloromethane with 0.1% triethylamine). The appropriate fractions

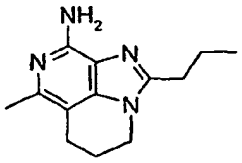
were combined and concentrated to afford 160 mg of 8-(aminomethyl)-3-propyl-5,6-dihydroimidazo[1,5-*a*]pyridine-1-carbonitrile as a colorless oil.

Part L

To a solution of 8-(aminomethyl)-3-propyl-5,6-dihydroimidazo[1,5-*a*]pyridine-1-carbonitrile (160 mg, 0.74 mmol) in ethanol (70 mL) in a glass pressure vessel was added 1 M HCl in diethyl ether (1.5 mL). The flask was sealed with a TEFLON cap and heated in a 110 °C oil bath. After 1 hour, additional 1 M HCl in diethyl ether (0.7 mL) was added. The flask was heated overnight. The solution was concentrated under reduced pressure and the crude product was purified by flash chromatography (silica gel, gradient elution with 5-10% methanol in chloroform with 0.1% ammonium hydroxide). The product was obtained as a white material that was triturated with dichloromethane and was subjected again to flash chromatography as described above to yield 116 mg of product that was crystallized form acetonitrile to give 53 mg of 2-propyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-9-amine as a pale rose solid, mp 166-170 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (t, 1, J = 0.9), 5.12 (br s, 2), 4.07 (m, 2), 2.80-2.89 (m, 4), 2.21 (m, 2), 1.78-1.91 (m, 2), 1.04 (t, 3, J = 7.3). MS (APCI) *m/z* 217 $(M + H)^+$. Anal. calcd for $C_{12}H_{16}N_4 \cdot 0.4\ H_2O$: C, 64.49; H, 7.58; N, 25.07. Found: C, 64.46; H, 7.48; N, 25.40.

Example 2

7-Methyl-2-propyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-9-amine



Part A

Ethyl 2-triphenylphosphoranylidene propionate (10.46 g, 28.9 mmol) was added to a solution of crude 5-iodo-1-(4-oxobutyl)-2-propyl-1*H*-imidazole-4-carbonitrile (prepared as described in Part E of Example 1, 28.9 mmol) in dichloromethane (100 mL). The solution was stirred at room temperature for 20 hours and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, gradient elution with 10-40% ethyl acetate/hexanes) to afford 6.35 g of ethyl (2*E*)-6-(4-cyano-5-

iodo-2-propyl-1*H*-imidazol-1-yl)-2-methylhex-2-enoate, which contained a small amount of an impurity but was carried on to the next step without further purification.

Part B

Nitrogen was bubbled through a solution of ethyl (2*E*)-6-(4-cyano-5-iodo-2-propyl-1*H*-imidazol-1-yl)-2-methylhex-2-enoate (6.21 g, 14.9 mmol) in DMF (50 mL) in a glass pressure vessel for 30 minutes, then triethylamine (3.13 mL, 22.4 mmol), palladium(II) acetate (165 mg, 0.75 mmol), and tris(2-methylphenyl)phosphine (685 mg, 2.24 mmol) were added. Nitrogen was bubbled through for five more minutes, then the flask was sealed with a TEFLON cap and heated in a 130 °C for 7.5 hours. The reaction mixture was allowed to cool to room temperature and was stirred overnight overnight. The reaction mixture was diluted with ethyl acetate and was washed with water (3x) and brine. The aqueous layers were back-extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude yellow oil was purified by flash chromatography (silica gel, gradient elution with 20-50% ethyl acetate/hexanes) to afford 2.90 g of ethyl 2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)acrylate as a yellow oil.

Part C

A mixture of ethyl 2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)acrylate (2.80 g, 9.76 mmol), $LiOH \cdot H_2O$ (1.64 g, 39.0 mmol), tetrahydrofuran (50 mL), methanol (25 mL), and water (25 mL) was stirred at room temperature for 2 days. The reaction was concentrated to about 25 mL under reduced pressure and 1 M HCl was added slowly (approximately 40 mL) until pH = 3 was obtained. The mixture was extracted with ethyl acetate (2x). The combined organic layers were washed with water and brine. A white solid in the organic layer was removed by filtration. The filtrate was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a white solid. The solids were combined to yield 2.42 g of 2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)acrylic acid.

Part D

Triethylamine (1.82 mL, 13.6 mmol) and diphenyl phosphoryl azide (2.62 mL, 12.1 mmol) were added to a 0 °C solution of 2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)acrylic acid (2.42 g, 0.33 mmol) in dichloromethane (90 mL). The magnetically stirred solution was allowed to warm to room temperature

over 40 minutes. The solution was concentrated under reduced pressure and the crude product was purified by flash chromatography (silica gel, stepwise elution with 20%, then 50% ethyl acetate/hexanes). The appropriate fractions were combined and concentrated under reduced pressure to afford 1.26 g of 2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)acryloyl azide.

Part E

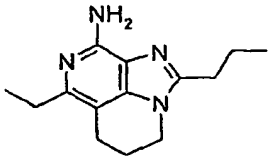
A solution of 2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)acryloyl azide (1.26 g, 4.43 mmol) in toluene (70 mL) was heated for 50 min at 90-100 °C. *tert*-Butyl alcohol (13 mL) was added and heating was continued for 14 hours. The solution was concentrated under reduced pressure. The residue was concentrated from toluene several times to provide a 2.31 g of a yellow oil which contained the product and toluene in about a 1:1 ratio by ^{1}H NMR. The mixture was used without purification in the next step.

Part F

Approximately 0.58 g of the material from Part E was dissolved in THF (70 mL) in a glass pressure vessel. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (7 mL) was added. The flask was sealed with a TEFLON cap and heated at 90 °C for 3 hours. Afterwards, the procedure was applied to the remaining material from the previous experiment. The batches were combined, concentrated, and purified by flash chromatography (silica gel, gradient elution 2-10% methanol/dichloromethane). The appropriate fractions were concentrated to afford a brown oil that solidified upon standing. The solid was triturated with dichloromethane/diethyl ether and was isolated by filtration. The filtrate was purified by flash chromatography to afford a solid that was also triturated with dichloromethane/diethyl ether and isolated by filtration. The solids were combined and crystallized from acetonitrile. Two crops of crystals were obtained and combined to yield 0.28 g of 7-methyl-2-propyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-9-amine as fluffy white crystals, mp 203-205 °C. ^{1}H NMR (300 MHz, $CDCl_3$ δ 5.13 (br s, 1), 4.02 (t, 2, J = 5.6), 2.82-2.78 (m, 4), 2.40 (s, 3), 2.25-2.17 (m, 2), 1.83 (sextet, 2, J = 7.5), 1.04 (t, 3, J = 7.5). MS (APCI) *m/z* 231 $(M + H)^+$. Anal. calcd for $C_{13}H_{18}N_4 \cdot 0.6\ H_2O$: C, 64.76; H, 8.03; N, 23.24. Found: C, 64.85; H, 8.45; N, 23.33.

Example 3

7-Ethyl-2-propyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-9-amine



Part A

Triethyl 2-phosphonopropionate (0.98 mL, 4.56 mmol) was added dropwise via syringe to a 0 °C mixture of potassium *t*-butoxide (0.512 g, 4.56 mmol) in THF (14 mL). The mixture was stirred at 0 °C for 30 minutes. The solution was added *via* cannula to a 0 °C solution of 5-iodo-1-(4-oxobutyl)-2-propyl-1*H*-imidazole-4-carbonitrile (prepared as described in Part E of Example 1, 1.00 g, 3.04 mmol) in THF (1 mL), followed by a THF rinse (3 mL). The reaction was allowed to warm to room temperature over 2 hours. Brine (15 mL) was added and the mixture was extracted with ethyl acetate (2x). The organic layers were combined and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, gradient elution with 20-40% ethyl acetate/hexanes) to afford 0.53 g of a mixture of ethyl (2*E*)-6-(4-cyano-5-iodo-2-propyl-1*H*-imidazol-1-yl)-2-ethylhex-2-enoate and the corresponding *Z* olefin isomer in a 4:1 ratio. The mixture was used in the next step.

Part B

The mixture of olefin isomers from the previous step (0.53 g, 1.24 mmol) was converted into ethyl (2*E*)-2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)but-2-enoate using the Heck reaction conditions described above. Additional portions of palladium(II) acetate and tris(2-methylphenyl)phosphine were added during the course of the reaction. The crude product was purified by flash chromatography (silica gel, gradient elution with 20-50% ethyl aceate/hexanes) to provide 0.27 g of a slightly impure 4:1 mixture ethyl (2*E*)-2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)but-2-enoate and the corresponding *Z* isomer.

Part C

Lithium hydroxide (0.149 g, 3.54 mmol) was added to a solution of a 4:1 mixture ethyl (2*E*)-2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)but-2-enoate

and the corresponding *Z* isomer (0.27 g, 0.88 mmol) in THF (4 mL), methanol (2 mL), and water (2 mL). The mixture was stirred at room temperature for 4 days, then was concentrated to about 4 mL under reduced pressure. The pH was adjusted with 1 M HCl to pH 3. The mixture was extracted with ethyl acetate (2x). The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to yield 0.33 g of (2*E*)-2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)but-2-enoic acid as an off-white solid that was used in the next step without purification.

Part D

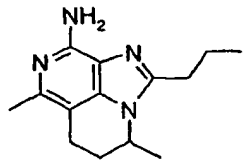
Diphenyl phosphoryl azide (0.228 mL, 1.06 mmol) was added to a mixture of (2*E*)-2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)but-2-enoic acid (approximately 0.88 mmol) and triethylamine (0.148 mL, 1.06 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to warm to room temperature and dichloromethane (2 mL) was added to form a solution. The solution was stirred at room temperature for 20 minutes. Additional diphenyl phosphoryl azide (0.5 mL) was added. After 10 minutes, the solution was concentrated and the residue was purified by flash chromatography (silica gel, 50% ethyl acetate/hexanes) to yield 0.15 g of (2*E*)-2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)but-2-enoyl azide as a colorless oil.

Part E

A solution of (2*E*)-2-(1-cyano-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-8-yl)but-2-enoyl azide (100 mg, 0.336 mmol) in toluene (13 mL) was heated for 55 minutes at 90 °C. The solution was concentrated under reduced pressure. The residue was dissolved in THF and transferred to a glass pressure vessel. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1 mL) was added. The vessel was sealed with a TEFLON cap and heated at 90 °C for 21 hours. The solution was concentrated under reduced pressure and purified by flash chromatography (silica gel, gradient elution with 2-10% methanol/dichloromethane) twice to yield a solid that was triturated with acetonitrile. The solid was isolated by filtration to yield 20 mg of 7-ethyl-2-propyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-9-amine as a white solid, mp 151-154 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (br s, 1.3), 4.03 (t, 2, J = 5.6), 2.84-2.78 (m, 4), 2.71 (q, 2, J = 7.5), 2.25-2.17 (m, 2), 1.83 (sextet, 2, J = 7.5), 1.26 (t, 3, J = 7.5), 1.04 (t, 3, J = 7.5). HRMS (ESI) calcd for $C_{14}H_{20}N_4$ 245.1766, found 245.1759.

Example 4

4,7-Dimethyl-2-propyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-9-amine



Part A

p-Toluenesulfonyl chloride (31.2 g, 164 mmol) was added to a 0 °C solution of 6-methyl-5-heptene-2-ol (20.0 g, 156 mmol) and pyridine (13.9 mL, 172 mmol) in dichloromethane (500 mL). The solution was stirred at room temperature for several days, then was poured into a separatory funnel and washed with ammonium chloride, water, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 40.2 g of 1,5-dimethylhex-4-enyl 4-methylbenzenesulfonate.

Part B

A mixture of 1,5-dimethylhex-4-enyl 4-methylbenzenesulfonate (40.2 g, 143 mmol) and sodium azide (10.2 g, 157 mmol) in dimethyl sulfoxide (DMSO) (300 mL) was heated at 80 °C for several hours, then was stirred at room temperature for 3 days. The reaction mixture was diluted to 1600 mL with water and was extracted with diethyl ether (4 x 300 mL). The organic layers were combined, washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 1,5-dimethylhex-4-enyl azide, which was carried on to the next step without further purification.

Part C

A mixture of the material from Part B (approximately 143 mmol), triphenylphosphine (74.4 g, 284 mmol), water (30 mL), and THF (500 mL) was heated at 45 °C for 30 hours, then was allowed to stand at room temperature for 2 days. The THF was removed under reduced pressure, and diethyl ether was added. The mixture was extracted with 1 M HCl (3x). The combined aqueous phases were washed with diethyl ether (2x), then were made basic with concentrated sodium hydroxide solution. The aqueous solution was extracted with diethyl ether (3x). The organic phases were

combined, washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 13.4 g of 1,5-dimethylhex-4-enylamine.

Part D

Triethylamine (15 mL, 106 mmol) was added to a suspension of aminomalonitrile *p*-toluene sulfonate (26.8 g, 106 mmol) in THF (500 mL). Trimethyl orthobutyrate (17 mL, 106 mmol) was added and the mixture was heated at reflux for 45 minutes, then was allowed to cool for 15 minutes. The crude 1,5-dimethylhex-4-enylamine from Part C (13.4 g, 106 mmol) was added and the solution was stirred at room temperature for 4 days. The solution was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The solution was extracted with water (2x) and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was purified by automated flash chromatography to yield 4.16 g of 5-amino-1-(1,5-dimethylhex-4-enyl)-2-propyl-1*H*-imidazole-4-carbonitrile.

Part E

A solution of 5-amino-1-(1,5-dimethylhex-4-enyl)-2-propyl-1*H*-imidazole-4-carbonitrile (1.00 g, 3.84 mmol) in chloroform (4.3 mL) was added over 20 minutes to an 80 °C solution of isoamylnitrite (1.03 mL, 14.4 mmol) in diiodomethane (13 mL). The reaction temperature did not exceed 90 °C during the addition. The dark red solution was heated at 80-90 °C for 15 minutes, then was allowed to cool to room temperature. The solution was concentrated under reduced pressure to afford an oil. This procedure was repeated with additional 5-amino-1-(1,5-dimethylhex-4-enyl)-2-propyl-1*H*-imidazole-4-carbonitrile (3.16 g, 12.1 mmol). The oils were combined and purified by automated flash chromatography (silica gel, gradient elution with 0-20% ethyl acetate/hexanes) to provide 2.6 g of 1-(1,5-dimethylhex-4-enyl)-5-iodo-2-propyl-1*H*-imidazole-4-carbonitrile.

Part F

Nitrogen was bubbled through a solution of 1-(1,5-dimethylhex-4-enyl)-5-iodo-2-propyl-1*H*-imidazole-4-carbonitrile (1.77 g, 4.77 mmol) and triethylamine (1.00 mL, 7.16 mmol) in DMF (16 mL) in glass pressure vessel. Palladium(II) acetate (26 mg, 0.12 mmol) and tris(2-methylphenyl)phosphine (109 mg, 0.36 mmol) were added and the vessel was sealed with a TEFLON cap. The vessel was heated in a 130 °C bath for 1.5 hours, then additional palladium(II) acetate (13 mg) and tris(2-methylphenyl)phosphine (55 mg) were added. The reaction was heated an additional 1.5 hours, then was allowed to

cool to room temperature. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by automated flash chromatography (silica gel, gradient elution with 2-30% ethyl aceate/hexanes) to provide 520 mg of a single diastereomer, whose structure was not assigned, of 8-isopropenyl-5-methyl-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-1-carbonitrile as a yellow oil that gradually solidified.

Part G

Ozone was bubbled through a -78 °C solution of 8-isopropenyl-5-methyl-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-1-carbonitrile (520 mg, 2.14 mmol) in dichloromethane (43 mL) until a pale blue color appeared. Methylsulfide (2 mL) was added. The solution was allowed to warm to room temperature and was concentrated under reduced pressure to yield crude 8-acetyl-5-methyl-3-propyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-1-carbonitrile, which was carried on to the next step without purification.

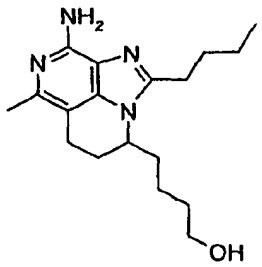
Part H

The material from Part G was dissolved in methanol (23 mL) in a glass pressure vessel. Ammonium acetate (455 mg, 2.5 mmol) and 7 M ammonia in methanol (1.7 mL, 5.9 mmol) were added. The vessel was sealed with a TEFLON cap and heated in a 90 °C oil bath for 14 hours. The solution was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was washed with water and brine. The aqueous layers were back-extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 0.38 g of a crude brown oil. The oil was triturated with ethyl acetate/hexanes and a solid formed that was isolated by filtration to afford 90 mg of 4,7-dimethyl-2-propyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-9-amine as a brown solid. A portion (ca. 40 mg) was purified by flash chromatography (silica gel, 0-20% CMA in chloroform) to afford about 20 mg of the product as an off white solid, mp 203-207 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (br s, 2), 4.55-4.50 (m, 1), 2.82-2.72 (m, 4), 2.37 (s, 3), 2.15-2.03 (m, 2), 1.88 (sextet, 2, J = 7.6), 1.33 (d, 3, J = 6.6), 1.04 (t, 3, J = 7.6). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 147.4,

143.2, 138.4, 123.4, 105.7, 47.3, 29.23, 29.15, 21.7, 20.5, 19.7, 17.1, 14.1. MS (ESI) *m/z* 245 $(M + H)^+$. HRMS (ESI) calcd for $C_{14}H_{20}N_4$ 245.1766, found 245.1781.

Example 5

4-(9-Amino-2-butyl-7-methyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-4-yl)butan-1-ol



Part A

Ethyl acetoacetate (12.8 mL, 100 mmol) was added dropwise to a slurry of sodium hydride (60% dispersion in oil, 4.40 g, 110 mmol) in THF (230 mL) at room temperature. The mixture was cooled to 0 °C for 15 minutes, then a solution of 2.5 M *n*-butyl lithium in hexanes (41.6 mL, 104 mmol) was added dropwise. The solution was stirred at 0 °C for 15 minutes, then 1-bromo-3-methyl-2-butene (12.1 mL, 104 mmol) was added at a rate such that the internal temperature remained between 5-10 °C. The solution was stirred for 45 minutes and 1 M HCl was added until an acidic pH was reached. The reaction mixture was allowed to warm to room temperature and was extracted with diethyl ether. The organic phase was washed with water until the washes had pH = 6. The organic phase was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield a yellow liquid. The liquid was purified by vacuum distillation (approximately 10 torr, 114-120 °C) to afford 12.4 g of ethyl 7-methyl-3-oxooct-6-enoate as a colorless liquid.

Part B

To a solution of sodium *t*-butoxide (5.66 g, 58.9 mmol) in ethanol (165 mL) at 0 °C was added dropwise ethyl 7-methyl-3-oxooct-6-enoate (12.4 g, 62.6 mmol). Sodium iodide (1 g) was added, followed by (3-bromopropoxy)(*tert*-butyl)dimethylsilane (14.4 g, 57 mmol). The mixture was heated at 80 °C for 2 hours, then at reflux for 5 hours, then at 70 °C for about 20 hours. The ethanol was removed under reduced pressure and the

residue was diluted with water and acidified to pH 3 with 1 M HCl. The mixture was extracted with diethyl ether (2x). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by automated flash chromatography (silica gel, gradient elution with 2-10% ethyl acetate/hexanes) to provide 14.1 g of ethyl 2-(3-{[*tert*-butyl(dimethyl)silyl]oxy}propyl)-7-methyl-3-oxooct-6-enoate as a colorless oil.

Part C

An aqueous NaOH solution (50% w/w, 3.33 g, 41.6 mmol) was added to a solution of ethyl 2-(3-{[*tert*-butyl(dimethyl)silyl]oxy}propyl)-7-methyl-3-oxooct-6-enoate (14.0 g, 37.8 mmol) in ethanol (100 mL) and water (10 mL). The solution was stirred at room temperature for 1 day, then additional 50% NaOH solution was added (about 2 grams), and the mixture was stirred for 5 days, The mixture was cooled in an ice bath and pH was adjusted with 1 M HCl to pH 6-7. The mixture was concentrated under reduced pressure to remove the ethanol. The remaining aqueous mixture was extracted with diethyl ether (3x). The organic layers were combined, washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 11.2 g of 1-{[*tert*-butyl(dimethyl)silyl]oxy}-9-methyldec-8-en-5-one.

Part D

Molecular sieves (3 Å) (8 g) followed by ammonium acetate (27.4 g, 35.6 mmol) were added to a solution of 1-{[*tert*-butyl(dimethyl)silyl]oxy}-9-methyldec-8-en-5-one (10.6 g, 35.6 mmol) in methanol (125 mL). The mixture was stirred for 10 minutes. Sodium cyanoborohydride was added. The flask was sealed with a rubber stopper and the mixture was stirred overnight. The mixture was filtered through CELITE filter agent and the filtrate was concentrated under reduced pressure. To the residue was added water (150 mL) and 5% aqueous NaOH solution (50 mL). The basic mixture (pH = 10) was extracted with dichloromethane (3x). To remove an emulsion, the organic layer was filtered through CELITE filter agent. The organic layer was washed with water and brine, dried over a mixture sodium sulfate and potassium carbonate, filtered, and concentrated under reduced pressure to yield 11.65 g of 1-{[*tert*-butyl(dimethyl)silyl]oxy}-9-methyldec-8-en-5-amine, which contained solvent. The calculated yield (based on ^{1}H NMR data) of the desired product was 9.96 g.

Part E

Trimethylorthovalerate (6.55 mL, 38.0 mmol) was added to a mixture of aminomalonitrile *p*-toluenesulfonate (4.81 g, 19.0 mmol) and pyridine (1.54 mL) in acetonitrile (65 mL) at room temperature. The reaction mixture was heated at 85 °C for 80 minutes. A solution of 1-{[*tert*-butyl(dimethyl)silyl]oxy}-9-methyldec-8-en-5-amine (8.53 g, 28.5 mmol) in acetonitrile (20 mL) was added and the solution was heated for an additional 1.5 hours, then was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The ethyl acetate layer was extracted with saturated aqueous sodium bicarbonate, water, and brine. The aqueous layers were back-extracted with ethyl acetate. The organic layers were combined and dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield a brown oil. The crude product was purified by automated flash chromatography (silica gel, gradient elution with 2-30% ethyl acetate/hexanes) to yield 4.5 g of 5-amino-2-butyl-1-[1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-5-methylhex-4-enyl]-1*H*-imidazole-4-carbonitrile as a brown oil.

Part F

A solution of 5-amino-2-butyl-1-[1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-5-methylhex-4-enyl]-1*H*-imidazole-4-carbonitrile (1.00 g, 2.24 mmol) in chloroform (2.5 mL) was added dropwise to a solution of isoamylnitrite (1.13 mL, 8.39 mmol) in diiodomethane (7.6 mL) at 80 °C. The temperature was not allowed to exceed 90 °C. The dark red solution was heated at 80-90 °C for an additional 15 minutes, then was allowed to cool to room temperature. The solution was concentrated under reduced pressure. The reaction was repeated using 4.50 g of 5-amino-2-butyl-1-[1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-5-methylhex-4-enyl]-1*H*-imidazole-4-carbonitrile. The residues from both reactions were combined and purified by automated flash chromatography (silica gel, gradient elution with 0-20% ethyl acetate/hexanes) to provide 3.22 g of 2-butyl-1-[1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-5-methylhex-4-enyl]-5-iodo-1*H*-imidazole-4-carbonitrile as an amber oil.

Part G

2-Butyl-1-[1-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-5-methylhex-4-enyl]-5-iodo-1*H*-imidazole-4-carbonitrile (2.22 g, 3.98 mmol) was converted into 600 mg of 3-

butyl-5-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-8-isopropenyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-1-carbonitrile using the Heck Reaction conditions described above (for example, in Part F of Example 1). The reaction was heated at 130 °C. The crude product was purified by automated flash chromatography (silica gel, gradient elution with 2-25% ethyl acetate/hexanes) to afford 0.60 g of a single diastereoisomer of 3-butyl-5-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-8-isopropenyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-1-carbonitrile as a yellow oil.

Part H

Ozone was bubbled through a -78 °C solution of 3-butyl-5-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-8-isopropenyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-1-carbonitrile (240 mg, 0.56 mmol) in dichloromethane until thin layer chromatography (TLC) analysis indicated the reaction was done. Methyl sulfide (0.5 mL) was added. The solution was stirred at –78 °C for 10 minutes, then was allowed to warm to room temperature. The solution was concentrated under reduced pressure, and then concentrated several times from methanol to afford crude 8-acetyl-3-butyl-5-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-1-carbonitrile, which was used in the next reaction without purification.

Part I

Ammonium aceate (120 mg) and 7 M ammonia in methanol (0.45 mL) were added to a solution of the crude material from Part H (approximately 0.56 mmol) in a glass pressure vessel. The vessel was sealed with a TEFLON cap and heated for 4 hours in a 90 °C oil bath. The solution was concentrated under reduced pressure. The crude product was purified by automated flash chromatography (silica gel, gradient elution with 1-40% CMA in chloroform) to yield 130 mg (54%) of 2-butyl-4-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-7-methyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-9-amine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (br s, 2H), 4.33 (m, 1H), 3.61 (t, J = 5.8 Hz, 2H), 2.88-2.65 (m, 4H), 2.40 (s, 3H), 2.40-2.27 (m, 1H), 2.01-1.91 (m, 1H), 1.88-1.76 (m, 2H), 1.67-1.36 (m, 8H), 0.97 (t, J = 7.2, 3H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 152.4, 147.3, 141.9, 138.5, 123.1, 105.6, 62.4, 51.8, 33.9, 32.4, 30.2, 26.9, 25.92, 25.85, 22.5, 22.4, 19.0, 18.2, 16.9, 13.8, -5.4. MS (APCI) *m/z* 431 $(M + H)^+$.

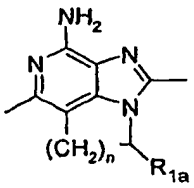
Part J

A solution of 2-butyl-4-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-7-methyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-9-amine (200 mg) in THF (2 mL), water (2 mL), and acetic acid (2 mL) was stirred for 24 hours. The solution was concentrated under reduced pressure, then was concentrated from methanol and toluene several times to provide crude 4-(9-amino-2-butyl-7-methyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-4-yl)butan-1-ol.

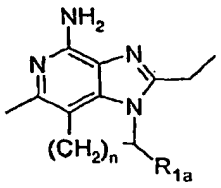
Alternatively, a mixture of 2-butyl-4-(4-{[*tert*-butyl(dimethyl)silyl]oxy}butyl)-7-methyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-9-amine (70 mg) and 1% concentrated hydrochloric acid in ethanol (10 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure, then was concentrated twice from methanol and once from methanol/acetonitrile. A white solid formed that was washed with acetonitrile, isolated by filtration, and dried under high vacuum to afford 31 mg of 4-(9-amino-2-butyl-7-methyl-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-1,6-naphthyridin-4-yl)butan-1-ol dihydrochloride hydrate, mp 187-198 (dec). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.2 (br s, 1), 7.98 (br s, 2), 4.60 (m, 1), 3.40 (t, 2, J = 5.8), 2.94-2.82 (m, 2), 2.80-2.63 (m, 2), 2.55-2.45 (m, 1), 2.38 (s, 3), 2.34-2.28 (m, 1), 1.92-1.78 (m, 3), 1.61-1.57 (m, 2), 1.49-1.34 (m, 6), 0.94 (t, 3, J = 7.3). ^{13}C NMR (500 MHz, DMSO-d_6) δ 155.0, 146.3, 139.3, 134.2, 120.2, 106.6, 60.3, 51.6, 32.9, 32.0, 28.8, 25.7, 24.6, 21.9, 21.8, 15.3, 14.9, 13.7. MS (APCI) *m/z* 317 $(M + H)^+$. Anal. calcd for $C_{18}H_{28}N_4O \cdot 2\ HCl \cdot H_2O$: C, 53.07; H, 7.92; N, 13.75; Cl, 17.40. Found: C, 53.17; H, 7.70; N, 13.72; Cl, 17.03.

Exemplary Compounds

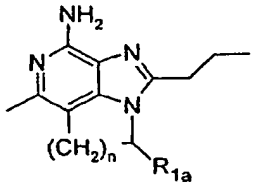
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (Ia, Ib, Ic, Id, Ie, If, Ig, or Ih) and the following R_{1a} substituents, wherein each line of the table is matched with Formula Ia, Ib, Ic, Id, Ie, If, Ig, or Ih to represent a specific embodiment of the invention.



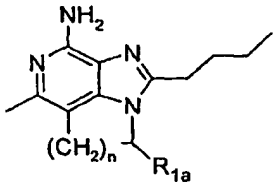
Ia



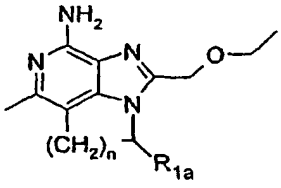
Ib



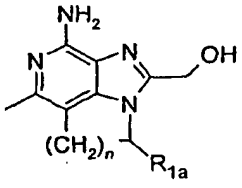
Ic



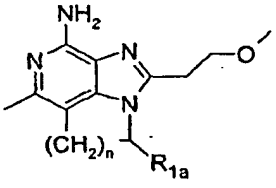
Id



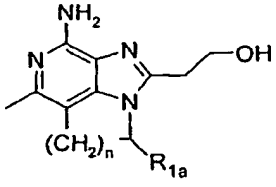
Ie



If



Ig

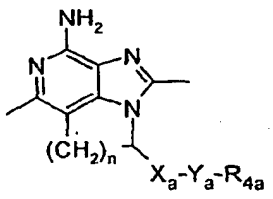


Ih

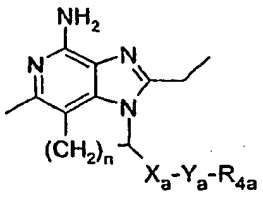
R_{1a}	n
hydrogen	2
methyl	2
isopropyl	2
1-fluoro-1-methylethyl	2
1-hydroxy-1-methylethyl	2
1-hydroxyethyl	2
2-hydroxyethyl	2
3-hydroxypropyl	2
4-hydroxybutyl	2
tetrahydro-2*H*-pyran-4-yl	2
(tetrahydro-2*H*-pyran-4-yl)methyl	

Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (Ii, Ij, Ik, Il, Im, In, Io, or Ip) and the following X_a

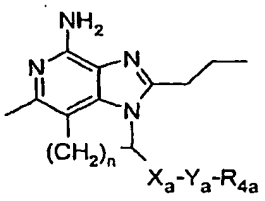
and $-Y_a-R_{4a}$ substituents, wherein each line of the table is matched with Formula Ii, Ij, Ik, Il, Im, In, Io, or Ip to represent a specific embodiment of the invention.



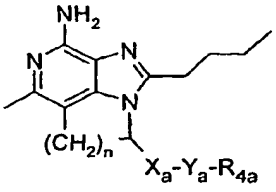
Ii



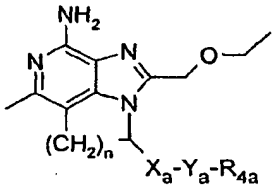
Ij



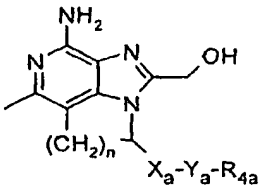
Ik



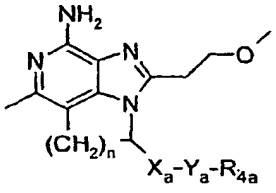
Il



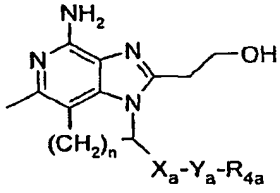
Im



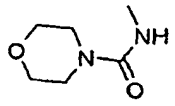
In

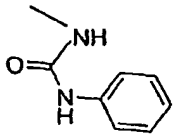
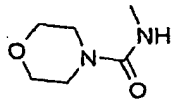
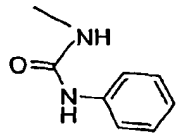
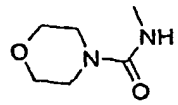
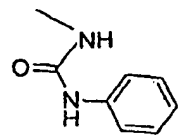


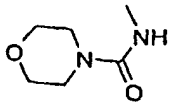
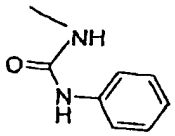
Io



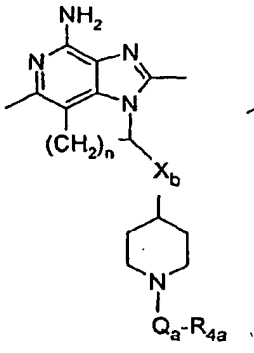
Ip

X_a	$-Y_a-R_{4a}$	n
$-CH_2-$	$-NH-S(O)_2-CH_3$	2
$-CH_2-$		2
$-CH_2-$	$-NH-C(O)-CH(CH_3)_2$	2
$-CH_2-$	$-NH-C(O)-CH_3$	2
$-CH_2-$	$-NH-C(O)-NH-CH(CH_3)_2$	2

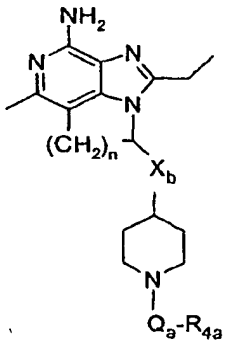
X_a	$-Y_a-R_{4a}$	n
$-CH_2-$		2
$-CH_2-$	$-NH-C(O)-N(CH_3)_2$	2
$-CH_2-$	$-S(O)_2-CH_3$	2
$-(CH_2)_2-$	$-NH-S(O)_2-CH_3$	2
$-(CH_2)_2-$		2
$-(CH_2)_2-$	$-NH-C(O)-CH(CH_3)_2$	2
$-(CH_2)_2-$	$-NH-C(O)-CH_3$	2
$-(CH_2)_2-$	$-NH-C(O)-NH-CH(CH_3)_2$	2
$-(CH_2)_2-$		2
$-(CH_2)_2-$	$-NH-C(O)-N(CH_3)_2$	2
$-(CH_2)_2-$	$-S(O)_2-CH_3$	2
$-(CH_2)_3-$	$-NH-S(O)_2-CH_3$	2
$-(CH_2)_3-$		2
$-(CH_2)_3-$	$-NH-C(O)-CH(CH_3)_2$	2
$-(CH_2)_3-$	$-NH-C(O)-CH_3$	2
$-(CH_2)_3-$	$-NH-C(O)-NH-CH(CH_3)_2$	2
$-(CH_2)_3-$		2
$-(CH_2)_3-$	$-NH-C(O)-N(CH_3)_2$	2
$-(CH_2)_3-$	$-S(O)_2-CH_3$	2

X_a	$-Y_a-R_{4a}$	n
$-(CH_2)_4-$	$-NH-S(O)_2-CH_3$	2
$-(CH_2)_4-$		2
$-(CH_2)_4-$	$-NH-C(O)-CH(CH_3)_2$	2
$-(CH_2)_4-$	$-NH-C(O)-CH_3$	2
$-(CH_2)_4-$	$-NH-C(O)-NH-CH(CH_3)_2$	2
$-(CH_2)_4-$		2
$-(CH_2)_4-$	$-NH-C(O)-N(CH_3)_2$	2
$-(CH_2)_4-$	$-S(O)_2-CH_3$	2

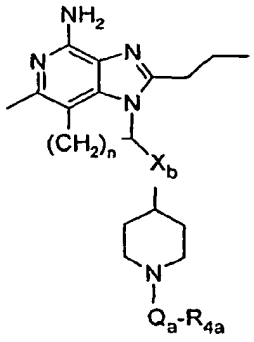
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (Iq, Ir, Is, It, Iu, Iv, Iw, or Ix) and the following X_b and $-Q_a-R_{4a}$ substituents, wherein each line of the table is matched with Formula Iq, Ir, Is, It, Iu, Iv, Iw, or Ix to represent a specific embodiment of the invention.



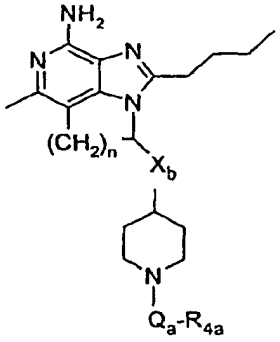
Iq



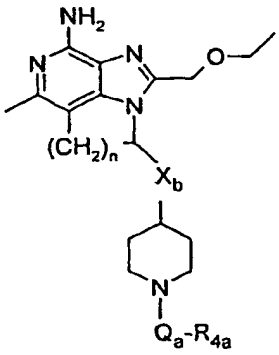
Ir



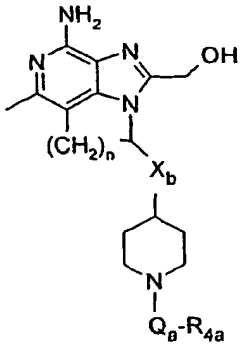
Is



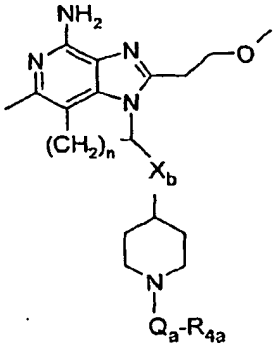
It



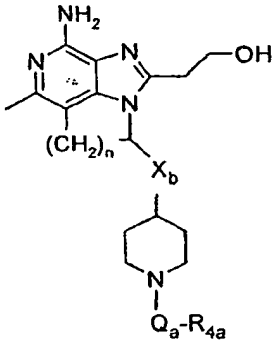
Iu



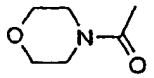
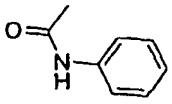
Iv

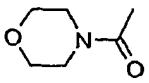
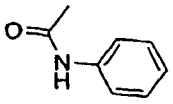


Iw

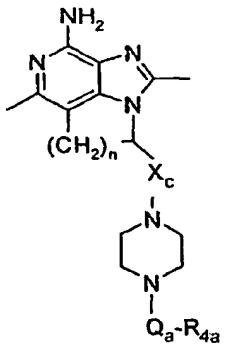


Ix

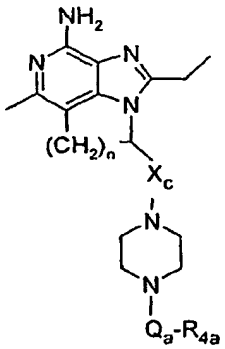
X_b	$-Q_a-R_{4a}$	n
bond	$-S(O)_2-CH_3$	2
bond		2
bond	$-C(O)-CH(CH_3)_2$	2
bond	$-C(O)-CH_3$	2
bond	$-C(O)-NH-CH(CH_3)_2$	2
bond		2
bond	$-C(O)-N(CH_3)_2$	2
$-CH_2-$	$-S(O)_2-CH_3$	2

X_b	$-Q_a-R_{4a}$	n
$-CH_2-$		2
$-CH_2-$	$-C(O)-CH(CH_3)_2$	2
$-CH_2-$	$-C(O)-CH_3$	2
$-CH_2-$	$-C(O)-NH-CH(CH_3)_2$	2
$-CH_2-$		2
$-CH_2-$	$-C(O)-N(CH_3)_2$	2

Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (Iy, Iz, Iaa, Iab, Iac, Iad, Iae, or Iaf) and the following X_c and $-Q_a-R_{4a}$ substituents, wherein each line of the table is matched with Formula Iy, Iz, Iaa, Iab, Iac, Iad, Iae, or Iaf to represent a specific embodiment of the invention.



Iy



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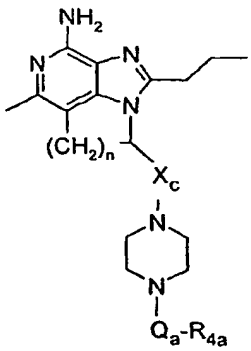

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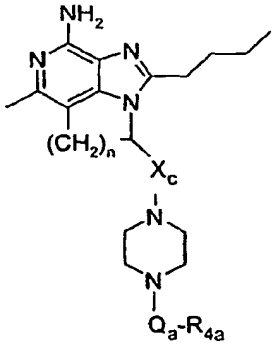

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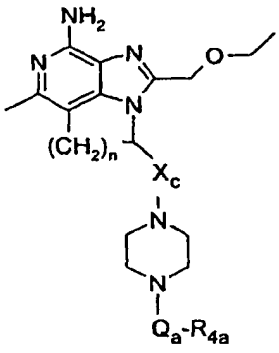

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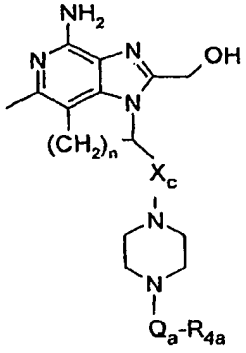

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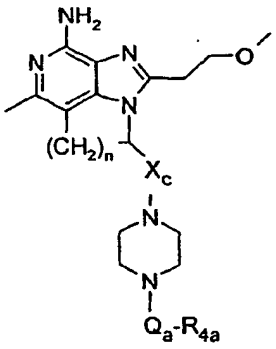

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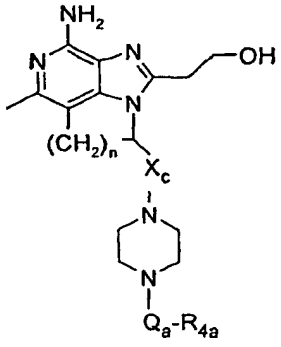
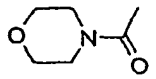
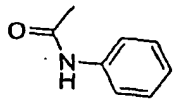


Iaf

5

X_c	$-Q_a-R_{4a}$	n
$-(CH_2)_2-$	$-S(O)_2-CH_3$	2
$-(CH_2)_2-$		2
$-(CH_2)_2-$	$-C(O)-CH(CH_3)_2$	2
$-(CH_2)_2-$	$-C(O)-CH_3$	2
$-(CH_2)_2-$	$-C(O)-NH-CH(CH_3)_2$	2
$-(CH_2)_2-$		2
$-(CH_2)_2-$	$-C(O)-N(CH_3)_2$	2

Compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α in human cells when tested using one of the methods described below.

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman *et al.* in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology, 58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences, Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4×10^6 cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then

added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4 °C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70 °C until analysis. The samples are analyzed for IFN-α by ELISA and for TNF-α by IGEN/BioVeris Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN-α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF-α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF-α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α and IFN-α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve.

The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

CYTOKINE INDUCTION IN HUMAN CELLS

(High Throughput Screen)

The CYTOKINE INDUCTION IN HUMAN CELLS test method described above was modified as follows for high throughput screening.

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences, Piscataway, NJ). Whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI complete (2-fold the final cell density). The PBMC suspension is added to 96-well flat bottom sterile tissue culture plates.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The compounds are generally tested at concentrations ranging from 30 - 0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with a reference compound 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) on each plate. The solution of test compound is added at 7.5 mM to the first well of a

dosing plate and serial 3 fold dilutions are made for the 7 subsequent concentrations in DMSO. RPMI Complete media is then added to the test compound dilutions in order to reach a final compound concentration of 2-fold higher (60 - 0.028 μM) than the final tested concentration range.

Incubation

Compound solution is then added to the wells containing the PBMC suspension bringing the test compound concentrations to the desired range (usually 30 - 0.014 μM) and the DMSO concentration to 0.4 %. The final concentration of PBMC suspension is $2x10^6$ cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 g) at 4 °C. 4-plex Human Panel MSD MULTI-SPOT 96-well plates are pre-coated with the appropriate capture antibodies by MesoScale Discovery, Inc. (MSD, Gaithersburg, MD). The cell-free culture supernatants are removed and transferred to the MSD plates. Fresh samples are typically tested, although they may be maintained at -30 to -70 °C until analysis.

Interferon-α and Tumor Necrosis Factor-α Analysis

MSD MULTI-SPOT plates contain within each well capture antibodies for human TNF-α and human IFN-α that have been pre-coated on specific spots. Each well contains four spots: one human TNF-α capture antibody (MSD) spot, one human IFN- α capture antibody (PBL Biomedical Laboratories, Piscataway, NJ) spot, and two inactive bovine serum albumin spots. The human TNF-α capture and detection antibody pair is from MesoScale Discovery. The human IFN-α multi-subtype antibody (PBL Biomedical Laboratories) captures all IFN-α subtypes except IFN-α F (IFNA21). Standards consist of recombinant human TNF-α (R&D Systems, Minneapolis, MN) and IFN-α (PBL Biomedical Laboratories). Samples and separate standards are added at the time of analysis to each MSD plate. Two human IFN-α detection antibodies (Cat. Nos. 21112 & 21100, PBL) are used in a two to one ratio (weight:weight) to each other to determine the IFN-α concentrations. The cytokine-specific detection antibodies are labeled with the SULFO-TAG reagent (MSD). After adding the SULFO-TAG labeled detection antibodies to the wells, each well's electrochemoluminescent levels are read using MSD's SECTOR

HTS READER. Results are expressed in pg/mL upon calculation with known cytokine standards.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α or IFN-α (y-axis) as a function of compound concentration (x-axis).

A plate-wise scaling is performed within a given experiment aimed at reducing plate-to-plate variability associated within the same experiment. First, the greater of the median DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. Negative values that may result from background subtraction are set to zero. Each plate within a given experiment has a reference compound that serves as a control. This control is used to calculate a median expected area under the curve across all plates in the assay. A plate-wise scaling factor is calculated for each plate as a ratio of the area of the reference compound on the particular plate to the median expected area for the entire experiment. The data from each plate are then multiplied by the plate-wise scaling factor for all plates. Only data from plates bearing a scaling factor of between 0.5 and 2.0 (for both cytokines IFN-α, TNF-α) are reported. Data from plates with scaling factors outside the above mentioned interval are retested until they bear scaling factors inside the above mentioned interval. The above method produces a scaling of the y-values without altering the shape of the curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91). The median expected area is the median area across all plates that are part of a given experiment.

A second scaling may also be performed to reduce inter-experiment variability (across multiple experiments). All background-subtracted values are multiplied by a single adjustment ratio to decrease experiment-to-experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on an average of previous experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-

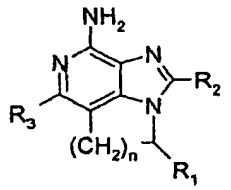
yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from an average of previous experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the Formula I:



I

wherein:

R_1 is selected from the group consisting of:

-X-R_4,

-X-Y-R_4,

-X-Y-X'-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkoxyalkyl, and hydroxyalkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-8} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkyl;

n is 1, 2, or 3;

X is selected from the group consisting of alkylene, alkenylene, and alkynylene, wherein the alkylene, alkenylene, and alkynylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

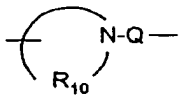
-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-C(R_6)-,
-O-C(O)-O-,
-N(R_8)-Q-,
-C(R_6)-N(R_8)-,
-O-C(R_6)-N(R_8)-,
-C(R_6)-N(OR_9)-,
-O-N(R_8)-Q-,
-O-N=C(R_4)-,
-C(=N-O-R_8)-,
-CH(-N(-O-R_8)-Q-R_4)-,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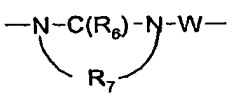
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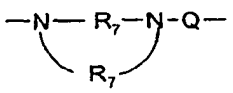
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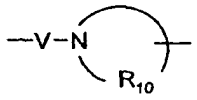
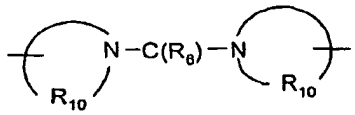
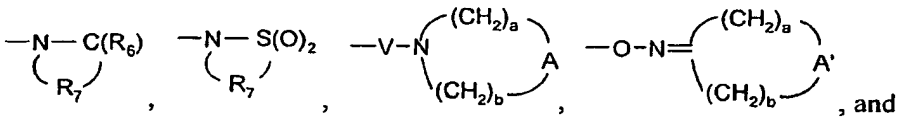

, and


;

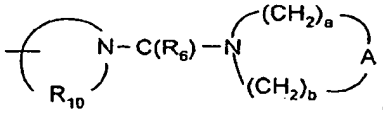
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino;

(dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; with the proviso that when R_4 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_4 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R_5 is selected from the group consisting of:



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -CH_2-, -O-, -C(O)-, -$S(O)_{0-2}$-, and –N(-Q-R_4)-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

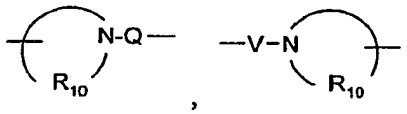
W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

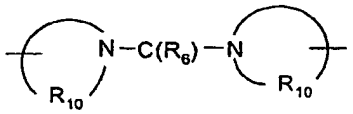
with the proviso that X can also be a bond when:

R_4 is bonded to X; or

Y is bonded to X and Y is -C(R_6)-, -C(R_6)-O-, -C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-, -C(=N-O-R_8)-, -CH(-N(-O-R_8)-Q-R_4)-,

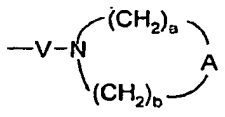


wherein V is -C(R_6)-, or

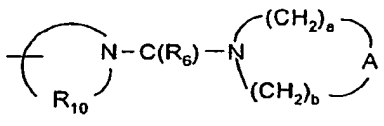


; or

R_5 is bonded to X and R_5 is



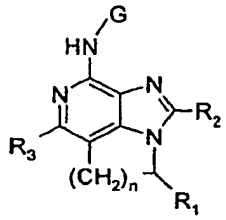
wherein V is -C(R_6)- or



;

or a pharmaceutically acceptable salt thereof.

2. A compound of the Formula II:



II

wherein:

G is selected from the group consisting of:

-C(O)-R',

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R',

-C(O)-N(R")R',

-C(=NY')-R',

-CH(OH)-C(O)-OY',

-CH(OC$_{1-4}$ alkyl)Y_0,

-CH_2Y_1, and

-$CH(CH_3)Y_1$;

R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl;

R_1 is selected from the group consisting of:

-X-R_4,

-X-Y-R_4,

-X-Y-X'-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkoxyalkyl, and hydroxyalkyl;

R_3 is selected from the group consisting of hydrogen, C_{1-8} alkyl, and C_{1-4} alkyl-O-C_{1-4} alkyl;

n is 1, 2, or 3;

X is selected from the group consisting of alkylene, alkenylene, and alkynylene, wherein the alkylene, alkenylene, and alkynylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

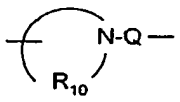
-$C(R_6)$-$N(OR_9)$-,

-O-$N(R_8)$-Q-,

-O-N=$C(R_4)$-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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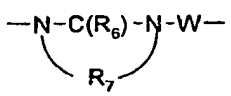

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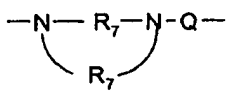

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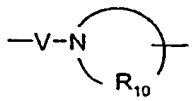
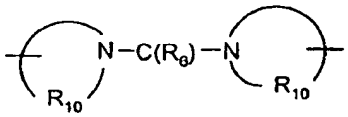
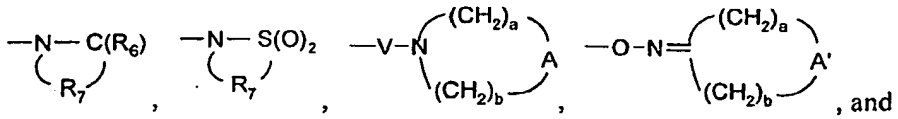
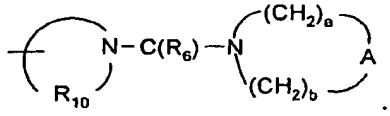

, and


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; with the proviso that when R_4 is aryl, arylalkylenyl, heteroaryl, or heteroarylalkylenyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, alkylarylenyl, alkoxyarylenyl, haloarylenyl, alkylsulfonylamino, arylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, heteroarylsulfonylamino, heteroarylcarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, and aryloxycarbonylamino; and with the further proviso that when R_4 is heterocyclyl, then the one or more substituents may also be independently selected from the group consisting of arylalkylenyl, and aminocarbonyl;

R_5 is selected from the group consisting of:


, and


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy-C_{1-10} alkylenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, aryl-C_{1-10} alkylenyl, and heteroaryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -CH_2-, -O-, -C(O)-, -$S(O)_{0-2}$-, and –N(-Q-R_4)-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

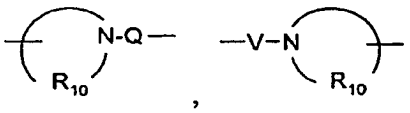
W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

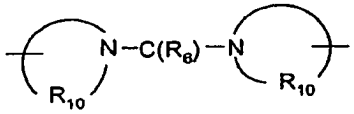
with the proviso that X can also be a bond when:

R_4 is bonded to X; or

Y is bonded to X and Y is -$C(R_6)$-, -$C(R_6)$-O-, -$C(R_6)$-$N(R_8)$-, -$C(R_6)$-$N(OR_9)$-, -C(=N-O-R_8)-, -CH(-N(-O-R_8)-Q-R_4)-,

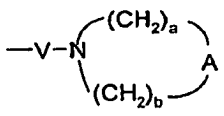


wherein V is -$C(R_6)$-, or

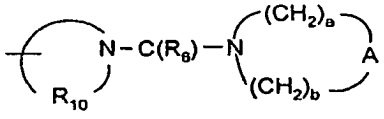


; or

R_5 is bonded to X and R_5 is



wherein V is -$C(R_6)$- or



;

or a pharmaceutically acceptable salt thereof.

3. The compound or salt of claim 1 or claim 2 wherein R_1 is -X-R_4.

4. The compound or salt of claim 3 wherein R_4 in -X-R_4 is alkyl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, and alkoxy.

5. The compound or salt of claim 4 wherein R_4 is C_{1-4} alkyl optionally substituted by hydroxy or one or more fluorine atoms.

6. The compound or salt of claim 3 wherein R_4 is aryl or heteroaryl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and dialkylamino.

7. The compound or salt of claim 3 wherein R_4 is tetrahydropyranyl.

8. The compound or salt of any one of claims 3 through 7 wherein X is a bond or alkylene.

9. The compound or salt of claim 8 wherein X is a bond.

10. The compound or salt of claim 8 wherein X is -CH_2-.

11. The compound or salt of any one of claims 3 through 6 wherein X is alkylene optionally interrupted by one or more -O- groups.

12. The compound or salt of claim 11 wherein X is C_{2-3} alkylene interrupted by one -O- group.

13. The compound or salt of claim 3 wherein R_1 is hydrogen.

14. The compound or salt of claim 3 wherein R_1 is methyl.

15. The compound or salt of claim 3 wherein R_1 is 4-hydroxybutyl.

16. The compound or salt of claim 3 wherein R_1 is tetrahydro-2*H*-pyran-4-yl or (tetrahydro-2*H*-pyran-4-yl)methyl.

17. The compound or salt of claim 1 or claim 2 wherein R_1 is -X-Y-R_4.

18. The compound or salt of claim 1 or claim 2 wherein R_1 is -X-Y-X'-Y-R_4.

19. The compound or salt of any one of claims 1, 2, 17, and 18 wherein Y is selected from the group consisting of -C(O)-, -$S(O)_2$-, -$N(R_8)$-Q-, or -C(O)-NH-.

20. The compound or salt of claim 19 wherein Q is -C(O)-, -$S(O)_2$, -$S(O)_2$-$N(R_8)$-, or -C(O)-$N(R_8)$-.

21. The compound or salt of any one of claims 17 through 20 wherein R_4 in Y-R_4 is alkyl, aryl, arylalkylenyl, or heteroaryl, wherein aryl, arylalkylenyl, and heteroaryl are optionally substituted by alkyl.

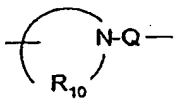
22. The compound or salt of claim 17 wherein Y is -S-, -$S(O)_2$-, or $N(R_8)$-Q- wherein Q is a bond, -$S(O)_2$-, -C(O)-, -C(O)-O-, -C(O)-$N(R_8)$-, -C(S)-$N(R_8)$-, or -$S(O)_2$-$N(R_8)$-; each R_8 is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxyC_{1-4} alkylenyl, and C_{1-4} alkoxyC_{1-4} alkylenyl; and R_4 is hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and dialkylamino.

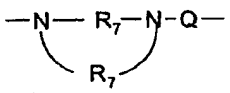
23. The compound or salt of claim 22 wherein Y is -NH-$S(O)_2$-, -NH-C(O)-, -NH-$S(O)_2$-$N(R_8)$-, -NH-C(O)-$N(R_8)$-, -NH-C(S)-$N(R_8)$-, -NH-C(O)-O-, or -$N(R_8)$-; and R_8 is hydrogen, methyl, ethyl, 2-hydroxyethyl, or 2-methoxyethyl.

24. The compound or salt of claim 22 wherein Y is -S- or -$S(O)_2$-, and R_4 is alkyl or aryl.

25. The compound or salt of anyone of claims 1 through 8 and claims 17 through 24 wherein X is -$(CH_2)_{1-3}$-.

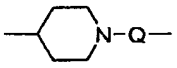
26. The compound or salt of claim 17 wherein Y is

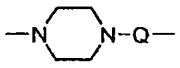


or


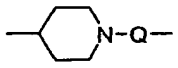
; Q is a bond, -C(O)-, -$S(O)_2$-, -$S(O)_2$-$N(R_8)$-, -C(O)-$N(R_8)$-, C(S)-$N(R_8)$-, or -C(O)-O-; R_7 is C_{2-3} alkylene; R_8 is hydrogen or C_{1-4} alkyl; R_{10} is C_{4-6} alkylene; and R_4 in Y-R_4 is hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, and haloalkyl.

27. The compound or salt of claim 26 wherein Y is



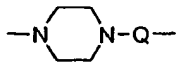
or


28. The compound or salt of claim 27 wherein X is a bond or -CH_2-, and Y is



29. The compound or salt of claim 28 wherein X is -CH_2-.

30. The compound or salt of claim 27 wherein X is -$(CH_2)_2$-, and Y is



31. The compound or salt of any one of claims 1 through 30 wherein R_2 is selected from the group consisting of hydrogen, alkyl, alkoxyalkyl, and hydroxyalkyl.

32. The compound or salt of claim 31 wherein R_2 is selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, methoxymethyl, ethoxymethyl, hydroxymethyl, 2-methoxyethyl, and 2-hydroxyethyl.

33. The compound or salt of any one of claims 1 through 32 wherein R_3 is hydrogen.

34. The compound or salt of any one of claims 1 through 32 wherein R_3 is methyl.

35. The compound or salt of any one of claims 1 through 34 wherein n is 2.

36. The compound or salt of any one of claims 1 through 34 wherein n is 3.

37. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 36 and a pharmaceutically acceptable carrier.

38. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 36 or the pharmaceutical composition of claim 37 to the animal.

39. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 36 or the pharmaceutical composition of claim 37 to the animal.

40. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 36 or the pharmaceutical composition of claim 37 to the animal.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/021839

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/16 A61K31/437 A61P31/00 A61P35/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 352 784 A (NIKOLAIDES NICK [US] ET AL) 4 October 1994 (1994-10-04) cited in the application claims; example 91	1-40

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2008	05/02/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bosma, Peter

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/021839

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 38-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/021839

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5352784 A	04-10-1994	DE 69426078 D1	09-11-2000
		DE 69426078 T2	13-06-2001
		EP 0708773 A1	01-05-1996
		ES 2150496 T3	01-12-2000
		JP 9500628 T	21-01-1997
		JP 3571342 B2	29-09-2004
		WO 9502598 A1	26-01-1995
		US 5444065 A	22-08-1995